DOCTOR OF PHILOSOPHY

EEG and fMRI studies of the effects of stimulus properties on the control of attention

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EEG and fMRI studies of the effects of stimulus properties on the control of attention

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DECLARATION

I declare that I am the author of this thesis, and unless otherwise stated, all references cited have been consulted by me. The work of which this thesis is a record has been carried out by myself and it has not previously been accepted for a higher degree.

Signed: …….

Carlos Andrés Mugruza Vassallo

I confirm, as thesis supervisor, that the conditions of the relevant Ordinance and Regulations for the Ph.D. degree have been fulfilled.

Signed: …….

Douglas D. Potter

DEDICATION

Tibi Deus, tutela meae familiae Sofi et Andres

Pater Raul, sempre ámat-t me

Mater Yolanda, sempre habitant cura-t et monet me

Meus frater et sorori et filis et filiabus aegre comitor convitus me quotidianus

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ABSTRACT

In this dissertation the effects of variations in stimulus properties and CTOA, in auditory attention tasks were explored using recently developed approaches to EEG analysis including LIMO. The last experiment was structured using information theory, designing an effective experiment. Four studies were carried out using a number parity decision task, that employed different combinations of cueing Tone (T), Novel (N) and the Goal (G) stimuli.

In the first EEG study, contrary to previous findings (Polich 2002, 2007) in control participants, no correlation between the time of a novel condition to the next novel condition and P300 amplitude was found. Therefore single trial across-subject averaging of participants' data revealed significant correlations ($r > .3$) of stimulus properties (such as probability, frequency, amplitude and duration) on P300, and even $r > .5$ was found when N was an environmental sound in schizophrenic patients.

In the second EEG study, simultaneously with fMRI recordings, the participants that showed significant behavioural distraction evoked brain activations and differences in both hemispheres (similar to Corbetta, 2002, 2008) while the participants, as a whole, produced significant activations mainly in left cortical and subcortical regions. A context analysis was run in distracted participants contrasting the trials immediately prior to the G trials, resulting in different prefrontal activations, which was consistent with studies of prefrontal control of visual attention (Koechlin 2003, 2007).

In the third EEG study, the distractor noise type was manipulated (white vs environmental sounds) as well as presence or absence of scanner background noise in a blocked design.

Results showed consistent P300, MMN and RON due to environmental noise. In addition, using time constants found in MEG results (Lu, Williamson & Kaufman, 1992) and adding the CTOA to the analysis, an information theory framework was calculated. After the simulation of the information of the experiment, a saddle indentation in the curve of the information measure based on the states of the incoming signal at around 300 ms CTOA was found. This saddle indentation was evident in more than 60 novel trials.

In the fourth study, the CTOA and stimulus properties were manipulated in a parametric experiment. Based on the three studies, reducing complexity if the task (first study), using more than 60 stimuli in the novel conditions (third study). The CTOA randomly varying between 250 ms or 500 ms. Thirty-eight ANCOVA with 2 categorical and 1 continuous regressors were conducted and determined which time and channels elicited reliably signatures ($p<.05$) in the whole participants at short CTOA. Results revealed differences for the waveforms of current condition by depending on which condition appeared previously as well in terms of frequency and duration in scalp frontal electrodes (such as the second study).

These results were interpreted as a consequence of switching between modes of attention and alerting states which resulted in the activation of frontal areas. Moreover, contextual analyses showed that systematic manipulation of stimulus properties allowed the visualization of the relationships between CTOA, executive function and orienting of attention.

Keywords: Attention, Electroencephalography (EEG), Event Related Potential (ERP), executive function, P300, MissMatch Negativity (MMN), Reorienting Negativity (RON), Cue-Target Onset Asynchrony (CTOA), Functional Magnetic Resonance Imaging (fMRI), Linear Modelling (LIMO); Orienting of attention, Stimulus properties.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

1.1 Motivation

In many aspects of everyday life we re-evaluate our current aims, monitor our behaviour and orient to novel events. We change or inhibit our behaviour according to the context of our thoughts and actions. At the centre of this complex framework of cognition are the mechanisms of attention control. The aim of this research is to better understand the circumstance in which novel events can cause orienting of attention.

Thus, drivers may be distracted by mobile calls or other external stimuli, airline pilots may be distracted by cockpit arrangements (*e.g.* Pasztor, 2010) or by internal thoughts during flight, and animals need to be aware when a new stimulus (*e.g.* a possible predator or natural catastrophe) occurs. All of these stimuli, from the point of view of potential reward or punishment, constitute salient signals to the brain. Thus, this stimulus-driven distraction that tends to promote a change/shift/reorienting of attention away from current goals may increase or decrease chances of survival. In order to study attention reorienting, we plan to study the ability of individuals to ignore auditory distracters while performing a simple goal driven task in a controlled environment. To improve our understanding of those brain areas involved in attention control as well as the timing sequence of those brain areas involved in the change/shift/reorienting attention task, I plan to use electroencephalography (EEG) and use the chance to combine in a multimodal approach electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). Having clarified the neurological basis of the EEG signals, a useful practical outcome would be to use EEG biomarkers with more precision and greater understanding of attention orienting.

1.2 Background

Research carried out by Donchin and colleagues led to the context updating theory (Donchin & Smith, 1970) of Event-Related Potentials (ERPs) around 300 miliseconds (ms) after a stimulus (P300). He also linked the ERP deflection with attention (Donchin & Isreal, 1980). Later, research carried out by Courschesne and colleagues (Courchesne, Hillyard & Galambos, 1975) suggested the P300 could be decomposed into the parietal P3b and a more frontal P3a evoked by novel events, this was reviewed extensively by Soltani and Knight (2000). Risto Näätänen linked the P3a to orienting of attention (Näätänen, 1991). There seems to be a general agreement that the P3b is a marker of context updating which may be preceded by attention orienting (P3a). According to Polich (Polich, 2007), the P3a (in frontal brain areas and modulated by dopamine) should be a biomarker of attention orienting to sensory input and P3b (in temporal/parietal brain areas and modulated by norephinephrine) should be a biomarker of memory storage subsequent to attention orienting. Level of attention demand can affect P300 amplitude measures, where task performance is governed by processing capacity and is modulated by arousal level (Polich, 2007) consistent with Kahneman's resources of attention (cited in Johnson and Proctor, 2004).

Usually P3a and P3b are elicited in an oddball paradigm. Figure 1 presents the typical ERP measure for the P300 in an easy stimulus discrimination, where the local probability of the standard (S) is 80% (p = .8) and the local probability of the target (T) is 20% (p = .2). A variant is shown in the form of a three-stimulus task, where Novel Distracter Stimuli show evoke higher amplitude more frontal P3a ERPs.

Several other ERP deflections are believed to mark the operation of distinct aspects of stimulus- and goal-driven attention:

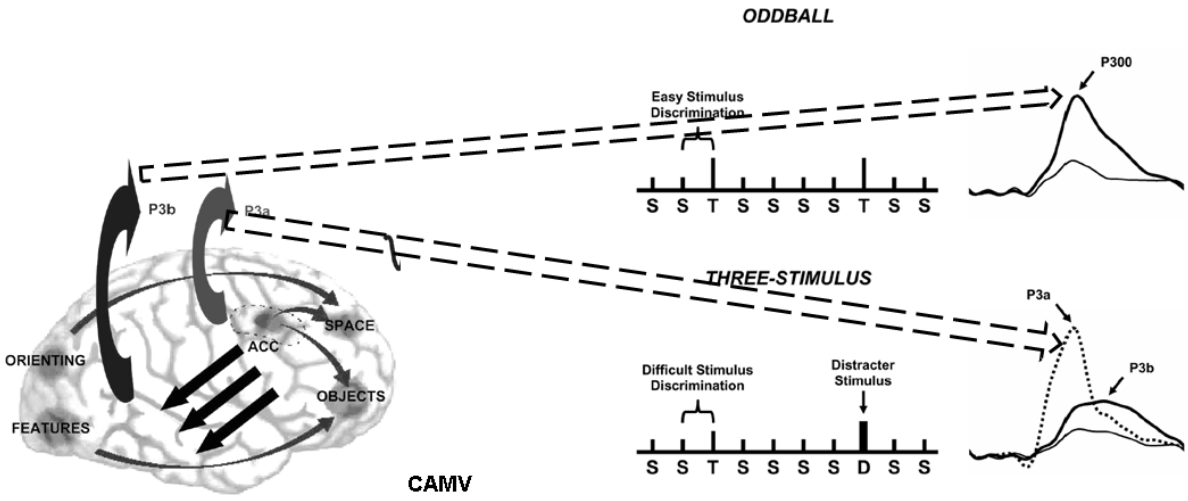


Figure 1 Auditory event-related potentials observed after several signal averaged. The stimulus produces an electrical signal that is averaged evoking P300 when the target is reached (modified from Polich, 1997).

The first ERP deflection, the MisMatch Negativity (MMN), originally reported by Näätänen, is the ERP believed to mark automatic detection of deviation of a stimulus from previously experienced stimuli by the auditory cortex and occurs in the 100 to 200 ms latency range (Näätänen, Gaillard & Mäntysalo, 1978). A typical experiment might use a standard stimulus frequency of 1 kHz with eight deviant sound frequencies in the range of 1005 to 1320 Hz. The participant's task, in the first blocks, was to monitor for infrequent deviant sounds without behavioural responses. In the final blocks behavioural responses were required and in this condition they found that the latency of MMN correlates with the participant's behavioural responses. Moreover, Tiitinen in Näätänen's group suggested that deviant stimulus detection depends on sensory memory mechanisms (Tiitinen, May, Reinikainen, & Näätänen, 1994). In a subsequent review of MMN the idea that episodic memory mechanisms, in terms of temporal stimulus features, stimulus duration, order of stimulus elements and patterns and sequence of stimuli, may be involved was introduced in recognition of the fact that ongoing experience is continually modifying our auditory perception of the world (Näätänen & Winkler, 1999). Similar mechanisms are believed to

operate in vision, but spatial dimensions may be more important (Treisman, 1988). MMN has also been observed in the visual modality with greater ERP deflection differences over the occipital temporal areas (Tales, Newton, Troscianko & Butler, 1999), but with less consistent durations and latencies than in auditory tasks (Pazo-Alvarez, Cadaveira & Amenedo, 2004). The MMN in the control participants is shown in Figure 2.

The Error Related Negativity (ERN or Ne) originally reported by Falkenstein, Gehring, Donchin and colleagues is a negative ERP deflection that appears shortly after errors and particularly after false alarms (Falkenstein, Hohnsbein, Hoormann & Blanke, 1991; Gehring, Coles, Meyer & Donchin, 1993). Ne was found first in Go-No-go tasks and using letters as stimuli showed a significant and large difference in ERP peaks in centro-parietal electrodes for visual tasks (Falkenstein et al., 1991). Ne is also found in the auditory modality with ERP deflections in fronto-central electrodes before the feedback occurs on error trials in the task (Falkenstein, Hoormann & Hohnsbein, 1999), consistent with internal monitoring mechanisms rapidly detecting the error. A further review of the Ne deflection in the context of the dopaminergic reward system and stimulus expectation can be found in the work of Brunia and colleagues (Brunia, Hackley, van Boxtel, Kotani & Ohgami, 2011). Recent work suggests important individual differences in dopamine neurotransmission and ERN combines the genetic and pharmacologic approaches conducted by Mueller and collaborators in a Flanker task experiment involving 169 male participants. Participants were genotyped by low (Val) and medium (Met) PFC dopamine levels and received a placebo or a sulpiride (a selective dopamine receptor blocker). EEG was decomposed using Independent Component Analysis (ICA). Val-participants who had received the placebo and Met participants who had received the sulpiride produced larger ERN deflections and greater response slowing in trials following errors compared with Val+ participants under sulpiride and Met/Met participants under placebo (Mueller, Makeig, Stemmler, Hennig & Wacker, 2011). This result gives an

explanation of how the different role of a neurotransmitter (dopamine) may produce different ERP results. And more importantly for the present study, ERN deflections are affected by genetic differences in groups and measures without group identification may support that the ERP responses of individual differences are due to different neurotransmitter distributions inside the brain. In the planned explorations of variability in ERP amplitudes or latencies differences across participants, i.e. either when they make more mistakes, or when considering individuals diagnosed with schizophrenia, it is important to bear in mind the possibility of individual differences in genotype.

A third ERP deflection, the ReOrienting Negativity (RON), is an ERP deflection which appears when the participant is engaged in a task and a distracting stimulus causes orienting to the new stimulus (P3a) and subsequent reorienting back to the goal stimulus (RON). The RON is a fronto-central negative-going ERP in the 400 to 600 ms latency range. For example, in a study by Schroger and Wolff in an auditory oddball task with probability of 0.1 and frequency deviance of 7% (Schroger & Wolff, 1998a), a P3a orienting response was followed by a RON. Schroger & Wolff suggested that the RON reflects the reorienting of attention to the original goal stimulus (Schroger & Wolff, 1998b). This ERP deflection appears for both auditory and visual modalities. It was reported for auditory oddball tones with +/- 50 Hz deviation in two equiprobable durations and for visual central triangles with change on position or orientation in two equiprobable durations (Berti & Schroger, 2001).

Bearing in mind the hypothesized association of dopamine with attention function, the attention deficit in schizophrenia (Shelley et al., 1991) and Parkinson's (Vieregge, Verleger, Wascher, Stüven, & Kömpf, 1994) patients and that Haloperidol is a dopamine D2-receptor antagonist that is widely used for the treatment of schizophrenia, Kähkönen and colleagues have tested the effects of dopamine receptor blockade on attention performance. Participants

were tested in an auditory oddball task with frequencies of 700 Hz and deviant stimuli of either 630 Hz or 770 Hz. Either Haloperidol or a placebo was administered to participants. They found amplitude reduction of P3a and RON in participants under haloperidol (Kähkönen *et al.*, 2002). Figure 2 (see lower figure) shows the RON in the participants under placebo and the reduction of RON under haloperidiol in the Cz electrode, but not clearly in the Pz electrode. Cz and Pz are shown because they are in the international 10-20 system for EEG.

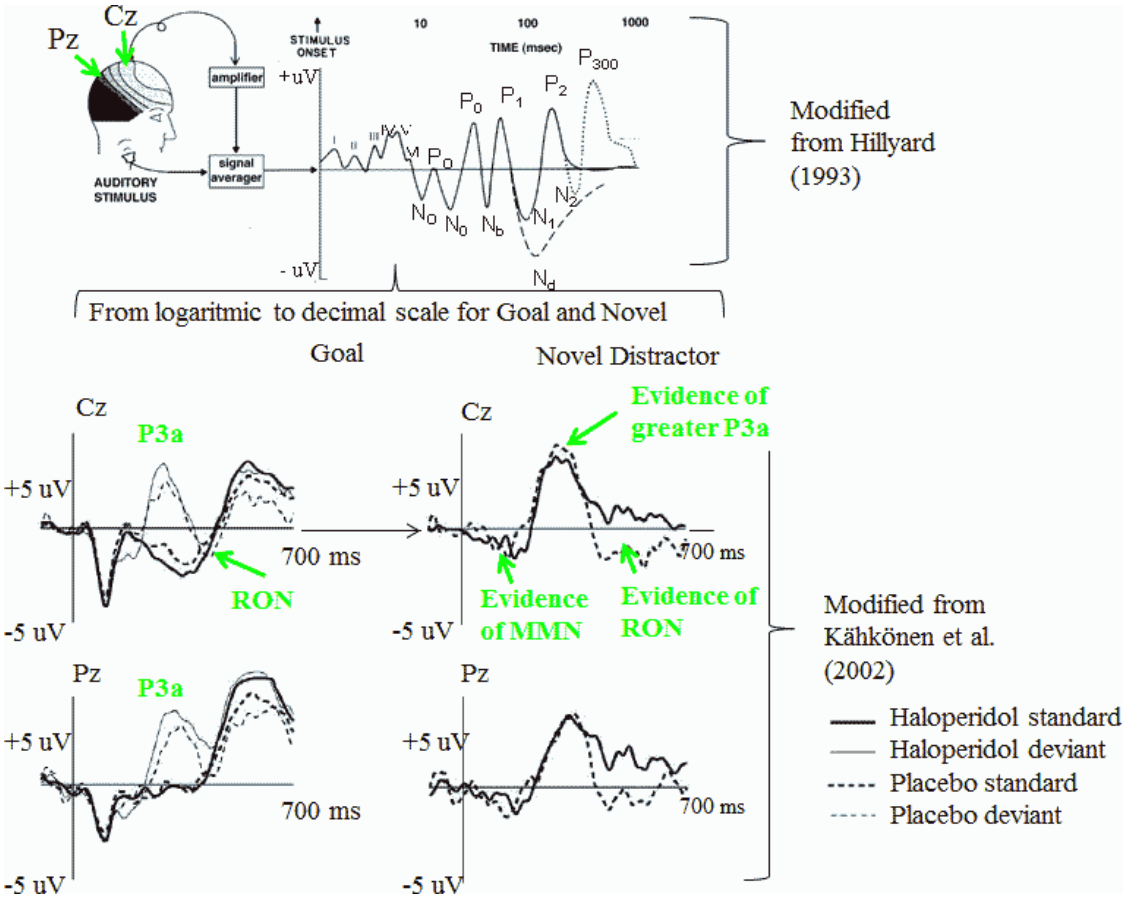


Figure 2 Upper plot: Illustration of EEG recording and averaging iluustrating auditory ERPs on logarithmic time scale (modified from Hillyard, 1993 and Picton, Hillyard, Krausz, & Galambos, 1974). Lower plot: This measure has been extended in the last decades for Goal stimulus, evoking N100 and no P300 in Pz electrode for Standard stimulus and Deviant stimulus evoking MMN, P3a and RON in Pz electrode e.g. results from Kähkönen et al.,

2002 illustrating the effects of haloperidol on response to goal stimuli and novel distractors (modified from Kähkönen et al., 2002).

ERPs provide useful non-invasive markers in the form of the P3a and P3b to distinguish between attention orienting and memory related processes and provide useful information regarding the timing of events but not in terms of the sources of this activity in the brain. With regard to brain sources of activity, EEG recordings by themselves have not provided good spatial resolution. In recent years methods such as LORETA (Pascual-Marqui, Esslen, Kochi & Lehmann, 2002, Pascual-Marqui, 2002) plus structural imaging have provided some insights into brain sources in epileptic seizures (Brodbeck et al., 2011; Vulliemoz et al., 2010). In the present research, the objective is to study spatial and temporal dynamics of the P3a response using combined EEG and fMRI. However, it has been observed that N1 and P2 responses are attenuated, but not P3a attenuated responses in the presence of scanner noise in an auditory oddball task (Mulert *et al.*, 2004).

Before the advent of fMRI and PET, important insights into the basic mechanisms of attention were made from animal studies in which responses to novel stimuli were studied in neurons in several regions of the auditory pathways including the Inferior Colliculus. For example, in the 1950s Rosenzwieg recorded the electrophysiological response of the auditory cortex in anaesthetized cats to study the balance between hemispheres to laterally presented sound in cats (Rosenzweig, 1954). In a further experiment they sought to determine if impulses from both ears interact in the inferior colliculi. Electrodes were placed in the Inferior Colliculus in anaesthetized cats after removal of the Cerebellum and a pair of stimuli in both ears with a time between stimuli (which can be taken as the Continuous Target Onset Asynchrony (CTOA) from 0 to 100 ms (Rosenzweig & Everett, 1955). Rosenzweig and Everett found that a temporal variation in CTOA of less than 20 ms in the binaural stimuli

leads to a greater electrophysiological inhibition of the response to the second stimulus. Stimulus-specific adaptation (SSA) may be induced in the typical oddball task with the deviant as the low probability stimulus, and then the response for the standard signal is attenuated after several repetitions in the cortical neurons (Ulanovsky, Las & Nelken, 2003).

More recently, Perez Gonzalez and colleagues sought to induce SSA at variable repetition rates from .5 to 5 stimuli per second. They designed a task that induced SSA in rats with blocks of 100 trials using standard signals of incremental frequencies from 7 kHz to 30 kHz. Some trials included a frequency different to the one expected, not producing incremental frequency and meaning a Novel stimulus in terms of the sequence of trials at every block. Electrodes were placed in the Inferior Colliculus. These neurons responded selectively to this Novel stimuli. Their response properties were consistent with the range of stimulation paradigms that produce MMN (Perez Gonzalez, Malmierca & Covey, 2005).

Moreover, research in animal studies now provides more insights into the relation between cortical and subcortical areas and some recent insights into the role of thalamocortical connections have been gained using auditory stimuli. Otazu and colleagues implanted tetrodes in rats in the auditory cortex and Thalamus in a double frequency discrimination 6 kHz and 24 kHz task. The discrimination task involved lateral auditory cues indicating which side the animal would receive water rewards. They found that engagement in the task suppressed responses in the auditory cortex, producing an attenuated signal compared to that elicited by selective attention. On the other hand, in the auditory Thalamus, engagement increased spontaneous firing rates but did not change evoked responses. This was explained by a thalamic modulation of cortical activity (Otazu, Tai, Yang & Zador, 2009). In population studies of GABA-ergic neurons in the thalamic reticular nuclei or medial geniculate body neuronal responses are stronger to deviant stimulus of 8 kHz compared to responses to the

standard stimulus of 14 kHz (Yu, Xu, He & He, 2009). These findings are from animal studies and caution is needed in translating them to human attention control. In animals there is only one GABA-ergic nucleus in the ganglionic eminence, but in primates there is also a GABA-ergic nucleus in the dorsal telencephalon (Petanjek, Kostovic & Esclapez, 2009). Therefore, there are potential limitations in making comparisons between animals and primates. In addition there are further differences in neuronal physiology and cortical organisation between human and primate brains.

Returning to purely human subjects, Gazzaniga has reviewed split-brain studies to observe the idea of right lateralized function in attentional monitoring and left lateralized function as an interpreter (Gazzaniga, 2000). Studies of the brain sources of visual attention mechanisms first showed some lateralisation to the right parietal cortex of sensitivity to non spatial targets and sustained attention (Coull & Nobre, 1998). Corbetta and Shulman (2002) propose that a stimulus-driven network involves ventral along with dorsal areas (Corbetta , Kincade, Ollinger, McAvoy & Shulman, 2000) and goal-driven network involving dorsal frontal and parietal areas (based on Bundesen, 1990). Subsequently, it was shown that higher visual working memory load results in a reduced sensitivity to novel stimuli (Shulman et al., 2003). Other experiments looked at whether Temporo-Parietal Junction (TPJ) activity is inhibited during goal-driven tasks in visual short-term memory and showed that high visual working memory loads suppress activity in the right TPJ (R TPJ) and that the R TPJ tends to activate stimulus-driven reorienting (Todd, Fougnie & Marois, 2005). On the basis of these and other experiments, Corbetta and collaborators propose a model of ¨reorienting¨ processing going from prefrontal to posterior areas of the cortex. In the model the goal-driven network includes the signals going from the dorsal network composed by FEF and IPS to visual areas and via a filtering signal through to the ventral network MFG. On the other hand, the model of the salience stimulus occurs in the stimulus-driven network that sends a reorienting signal

through MFG to the dorsal network composed by IPS and FEF in the exogenous orienting signals (Corbetta, Patel & Shulman, 2008). Recent metaanalysis has sought for parts of the TPJ in reorienting of attention in 25 studies and in theory of mind in 29 studies using activation likelihood estimation. The results suggested a more specific the role of the anterior R TPJ in attention and theory of mind while the posterior part of the R TPJ is involved in theory of mind (Krall et al., 2014) (see Figure 3).

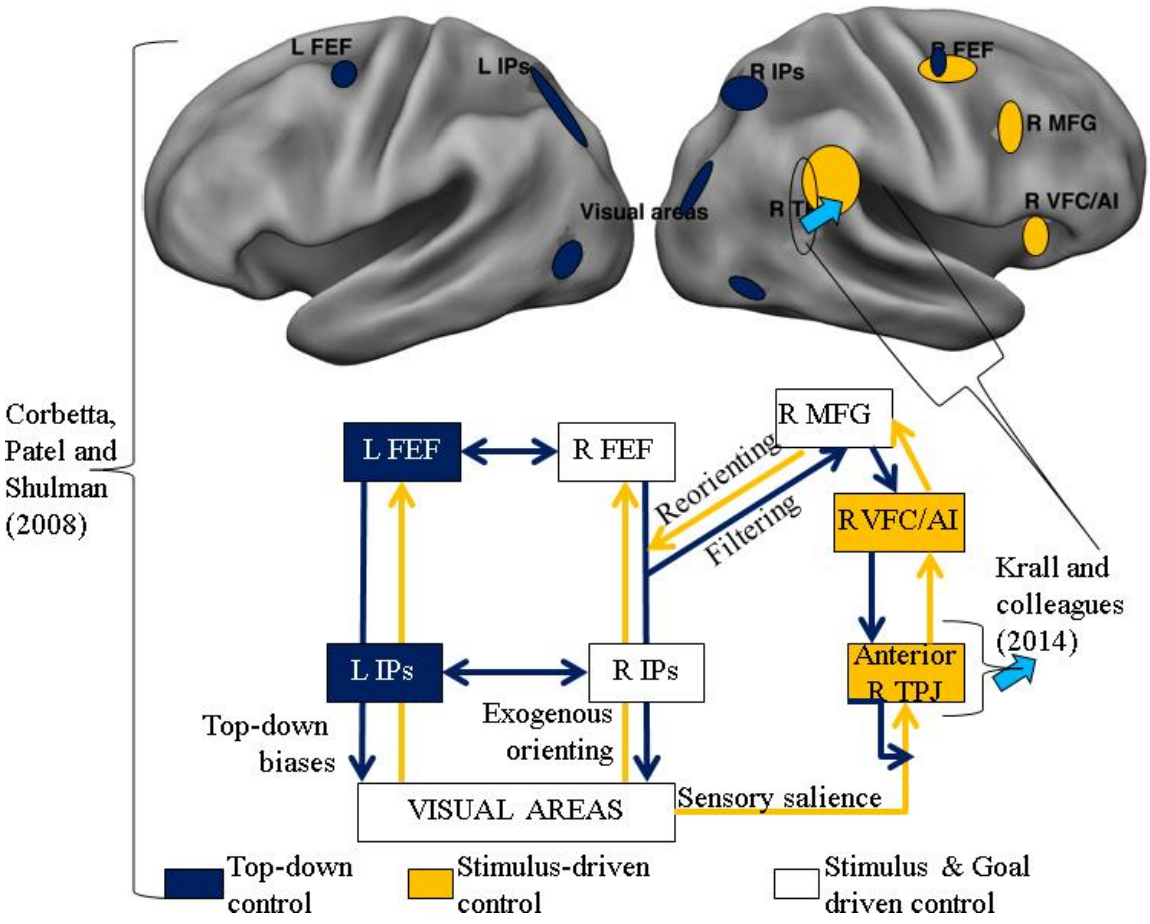


Figure 3 Stimulus and Goal-driven control networks of attention, modified from meta-analysis results of Corbetta et al. (2008) and Krall et al. (2014). Regions in blue and white are activated by central cues, facilitating a faster activation by the upcoming stimuli. Regions in yellow and white are activated when attention is reoriented to an unexpected but behaviourally relevant object.

The idea that attentional selection can be based on either an internal goal-based model or on a more stimulus driven mechanism has a long history. In an early experiment, Tanner and Norman (1954) studied selective attention using the 'receptor theory' signal detection framework to test whether a single or dual mechanism model best explains auditory human attention. Sounds at an unexpected frequency are more difficult to detect than those at an expected frequency. They employed two experiments. The first, in which a tone embedded in white noise was presented simultaneously with one of four light flashes. After a number of trials participants could detect the target 65% of the time. If a tone of a new frequency was presented instead, participants were initially unaware of the new tone. In the second task a standard tone and a new tone were presented sequentially with an ISI of 50 ms where tone frequencies and sound durations can change and the participant was asked to identify whether the standard tone was present. They found that the performance of the participants again decreased to chance levels. They argued that this result supports the view that a dual mechanism is involved in signal reception, a "narrow-band panoramic receiver" that tuned to the required or target signal or a "wide open receiver" for the detection of any signal (Tanner & Norman, 1954). These two mechanisms are reminiscent of the GDN and SDN respectively that have been proposed by Corbetta and Shulman in 2002.

The importance of timing of stimulus events in attention control was explored in the 1990s using PET and fMRI. For example, Coull and Nobre (1998) explored the role of temporal cues in visual attention. When subjects were required to estimate time intervals of either 300 ms or 1500 ms after visual cue presentation, the authors found several common areas for both spatial and temporal conditions of the task with some hemispheric lateralisation where these conditions are compared to the right and left, respectively (Coull & Nobre, 1998). Recent behavioural studies by Sanabria and colleagues have explored the properties of stimulus-

driven attention network by using 2 different CTOAs in separate visual and auditory experiments. They found that the short CTOA would speed reaction times (RT) and the longer CTOA would produce slower reaction times (Sanabria, Capizzi & Correa, 2011). The interpretation is that the CTOA and local probability in the stimulus presentation modulates the RT in the goal attention task. However, these findings match with the optimal timing ranges for exogenous (100 to 300 ms) and endogenous (more than 400 ms) cues in orienting of attention (Wright & Ward, 2008).

It is evident that different researchers are using the terms orienting and reorienting in different ways. In the present research the following interpretations of these terms will be adopted. "Orienting of attention" following the ERP waves that were studied initially by Sokolov P3a (Sokolov, 1963). Visual orienting can be overt, by means of eye movements and covert via shifts of the focus of attention (Posner, 1981). The interpretation of "Reorienting negativity" is taken here as the same as the ERP deflection that was studied by Schroger and Wolff (Wolff & Schroger, 1998a, 1998b).

Posner and colleagues developed a model of attention based on three phases: disengage, moving attention and engagement of attention with the target (Posner, Walker, Friedrich & Rafal, 1984). Nissen and Corkin, using an auditory warning signal followed by a visual target, found slower RTs in older people than in younger people. Moreover, the unexpected targets produced more cost in terms of RTs in older participants and mean RTs were longer for older people at first block while it was constant across blocks for younger participants. They interpreted that the small local probability of an exogenous cue can cause "Reorienting of attention" in older people than in younger people (Nissen & Corkin, 1985).

"Reorienting" is interpreted as orienting of attention to the same location that has been the previous focus of attention (Harman, Posner, Rothbart & Thomas-Thrapp, 1994). More recently, Corbetta and colleagues consider that the "reorienting response" is the complex set of adjustments in response to novel and unexpected stimuli (Corbetta et al. 2008).

The typical oddball experiments include standard non-target (*e.g.* $p = .8$) and deviant targets (*e.g.* $p = .2$). The three-stimulus oddball task includes the standard (*e.g.* $p = .8$), the deviant target (*e.g.* $p = .2$), and the distractor (*e.g.* $p = .1$) (for a review see Polich, 2007). Therefore, in the experiments addressed in oddball tasks, we can consider orienting as a result of the voluntary focus of attention to a particular task (the infrequent target in the 3 oddball paradigm) and the term reorienting can relate more precisely to the unexpected stimulus (the novel distractor in the 3 oddball paradigm).

It is intended in the present research to use EEG recordings to provide more detailed information about the timing of attention related brain events using a common general linear modelling approach to the analysis of single trial data. In this way, time course by linear regression analysis was done initially in visual word recognition by analysis using a regressor coefficient (Hauk, Ford, Pulvermuller & Marslen-Wilson, 2006). A further use of this approach in EEG analysis is a recent study of face processing (Rousselet, Pernet, Bennett & Sekuler, 2008). In the first block, participants had to decide face identity between two faces, and in the second and third block between two pink and wavelet noise visual textures. Phase coherence was systematically manipulated in the images to make the identity more difficult to discern. This approach demonstrated that the largest EEG fluctuations that related to the phase manipulation occurred between the typically identified mean ERP features in the posterior region of the head. The analysis employed the LIMO toolbox, a general linear

model to study brain waves, relying on the statistical testing and resampling using matrix modelling based on a single predefined predictor (Pernet, Chauveau, Gaspar, & Rousselet, 2011). They tested their LIMO analysis in 18 subjects with a similar identity face task to that of Rousselet and colleagues and they found congruent results in the time range of 140 ms to 170 ms with $p<.05$ across the electrodes in the posterior part for individual and group analysis (Rousselet et al., 2008).

This general linear modelling approach contrasts, for example, with single trial analysis based on independent component analysis (ICA, first used in Makeig, Jung, Bell, Ghahremani & Sejnowski, 1997), where trial sequence is accounted fot in the analysis. An important area of development that can be used or improved is in the combined analysis of EEG and fMRI data (Debener, Ullsperger, Siegel & Engel, 2006), with powerful methods and toolboxes to remove Magnetic Resonance (Brain Vision Analyzer version 1.05.0001) and electrocardiogram (ECG, Niazy, Beckmann, Iannetti, Brady & Smith, 2005) artifacts from EEG data.

One of the aims of this research described in this thesis is to use the spatial resolution of fMRI to identify sources of activation, and simultaneously to combine this with EEG recording to provide more detailed information about the timing of brain events using a common general linear modelling approach to the analysis of single trial data to test specific hypotheses about the sources of the attention related ERP markers.

1.3 Problem Formulation

We can begin the formulation of the problem having general limitations and points of view with our proposed paradigm as follows:

First, at a Psychological level (Function), can we find a cognitive architecture that captures the details of the human reorienting system in a specific cognitive task?

The current visual reorienting model (Corbetta et al., 2002, 2008) does not take into account the subcortical regions and the functional activity or response of several properties and dynamics of auditory and visual events. Therefore, within those several possibilities or pathways of brain sources and dynamic of the Regions Of Interest (ROI) to analyse, there are typical activation patterns in ROI when the participant is engaged in a specific cognitive task with distractors. Recent research suggests that the thalamic connections, Thalamus and Thalamic Reticular Nuclei (TRN) may play an important role in attention through connections with the cortex (see review of Alonan & Brown, 2002). For example, in EEG recordings in controls and schizophrenic patients, an attenuation was found in centroparietal EEG frequency content between 13.75 and 15 Hz. This was interpreted as an impairment of the sleep spindle which was linked with a further impairment in the TRN (Ferrarelli et al., 2007). Next Ferrarelli's proposal, bearing in mind this result, is that of using TRN and other GABA-ergic brain areas with NMDA receptors to formulate a further model of NMDA receptor with different layers (namely Thalamus, TRN and Layers 4-6 in the cortex) in the brain for schizophrenic patients (Ferrarelli & Tononi, 2011). A specific study focusing on auditory tasks is an architecture for stimulus processing considering TRN, Thalamus, auditory cortex and prefrontal cortex to differentiate controls from schizophrenic patients by means of TRN control of the Thalamus (Du & Jansen, 2011). Therefore, the Ferrarelli's approach captures the NMDA neurotransmitter signalling and the Du and Jansen's model for different dopamine signalling across different brain areas not only in healthy controls but also in schizophrenic patients. However, the cognitive architecture for novel auditory sounds is

not fully developed in these papers.

Second, at an algorithmic level: what operations do we need to perform *e.g.* engage, disengage, orient, reengage, etc. Therefore, can we describe the functionality of its brain areas or parts related with each operation? Or in other words, can we find a cognitive architecture that explains how humans manage attention against salient stimuli to reorient attention and maintain a high level of intellectual attention function in a cognitive decision task?

An examination of the general background has shown that, on the one hand, the visual system has been studied using several methods including EEG and fMRI and depending on the stimulus type, involves activation of several areas in the brain. On the other hand, auditory research has produced extensive work on the literature of orienting attention with auditory stimuli in tasks that points out to single tones (Kiehl et al., 2005; Mulert et al., 2004), which are tasks without an abstract information meaning as one finds in everyday life. Moreover, keeping in mind those different tasks proven in the case of rats (*e.g.* Perez Gonzalez et al., 2005), it can be said that these tasks are based on sound frequencies or sound durations (*e.g.* Tiitinen et al., 1994; Gonsalvez & Polich, 2002; Mulert et al., 2004, etc). Alternative, more complicated paradigms have been employed, for example attention to multiple tone patterns (Boh, Herholz, Lappe, & Pantev, 2011), dichotic listening (Westerhausen et al., 2010) or tasks that divert attention with a secondary task (*e.g.* the McGurk effect in Colin, Radeau, Soquet & Deltenre, 2004). In this way, there is not a better test of the typical description once the stimulus reaches the participant: a salient event triggers the alerting in the left hemisphere or orienting of attention in the right hemisphere, and this effect is influenced by the participant's capacity to manage working memory load. Although both parity decision tasks and numerical tasks are quite well studied (*e.g.* Otten, Sudevan, Logan & Coles, 1996),

recent works suggest that the previously presented numbers should introduce a change in the reaction time depending on the magnitude of the previously presented Visual number stimulus (Santens & Gevers, 2008). In the present research, an auditory number parity decision task was chosen because it is not very complex but does require concentration to perform the task and avoid mistakes. Therefore, it is postulated that it can allow the measurement and study of changes in attention orienting without significant confounds related to reward effects.

Third, at a Biological level (Instantiation), can we find a neurological architecture that corresponds to what we know about the reorienting of attention in the brain?

The current visual reorienting model of attention (Corbetta et al., 2002, 2008) does not take into account subcortical regions and only notes the difference in activation when stimuli are present or not present in average blocks (fMRI limitation) and does not take into account the dynamic properties of the stimuli, for example temporal changes in the stimulus presentation. In other words, current cognitive models often do not consider the influence of local variations in stimulus probability or stimulus variability on models of both EEG waves and hemodynamic response in fMRI. These models consider logic steps seeking to reproduce a very simplified oddball task without taking into account brain areas of activation (e.g. Friston, 2005) and more realistic in terms of brain areas but without having been tested on cognitive tasks (Bojak, Oostendorp, Reid, & Kötter, 2009; Coombes, 2010), although there are recent insights in associating spontaneous with evoked activity in a neural mass model of cat visual cortex (Trong, Bojak, & Knösche, 2013).

Technologically / Methodologically: Can we use multimodal techniques such as combined

EEG and fMRI to study the dynamics of the orienting of attention? EEG has good temporal resolution but limited spatial resolution. On the other hand, fMRI has good spatial resolution but the temporal resolution is limited by the rate of the haemodynamic response. Thus, in principle, we should be able to correlate EEG and fMRI signals in such a way that we can use the latter to analyse EEG sources while at the same time gaining insight into the timing of activity in these identified regions of activity in the fMRI data.

By taking these different points of views into account, this research enables consideration of several problems. As can be followed by the highlighted blocks in Figure 4, the aim of this research is to test models of attention in cognitive tasks, providing an approach of predictions in attention and having methods to provide better accuracy regarding the dynamics of brain networks based on both optimized analysis of EEG data and minimizing the uncertainty of combined EEG/fMRI.

Focusing on the problems (questions/difficulties) that this research is going to involve, a tree of problems is illustrated in Figure 4 with numbers in parenthesis: (10) Limited methods to study continuous waves with electroencephalography (EEG) recording, having sensitivity of current techniques to movement artifacts, (20) temporal limitation of functional magnetic resonance imaging (fMRI) recordings; (30) spatial limitation in resolution of EEG recordings; and (4) temporal limitation to study dynamics. Based on these three problems (40) the cross-modal effect of running simultaneous/combined EEG/fMRI create noisy/blurred MRI near to the skull and electromagnetic noise in EEG recordings. Adding the previous four problems there is (50) uncertainty about experimental dynamics of brain areas in orienting of attention. On the other hand (60) makes it difficult to test models of attention in high cognitive tasks and give a posterior (70) complex prediction of behaviour and

attention. Both (50) uncertainty dynamics and (70) complexity behaviour and attention in humans give (80) an incomplete comprehension of orienting attention and conveys to (90) an incomplete comprehension of dysfunctions in attention and further less understood ways to differentiate healthy participants and people with potential attention disorders (see Figure 4).

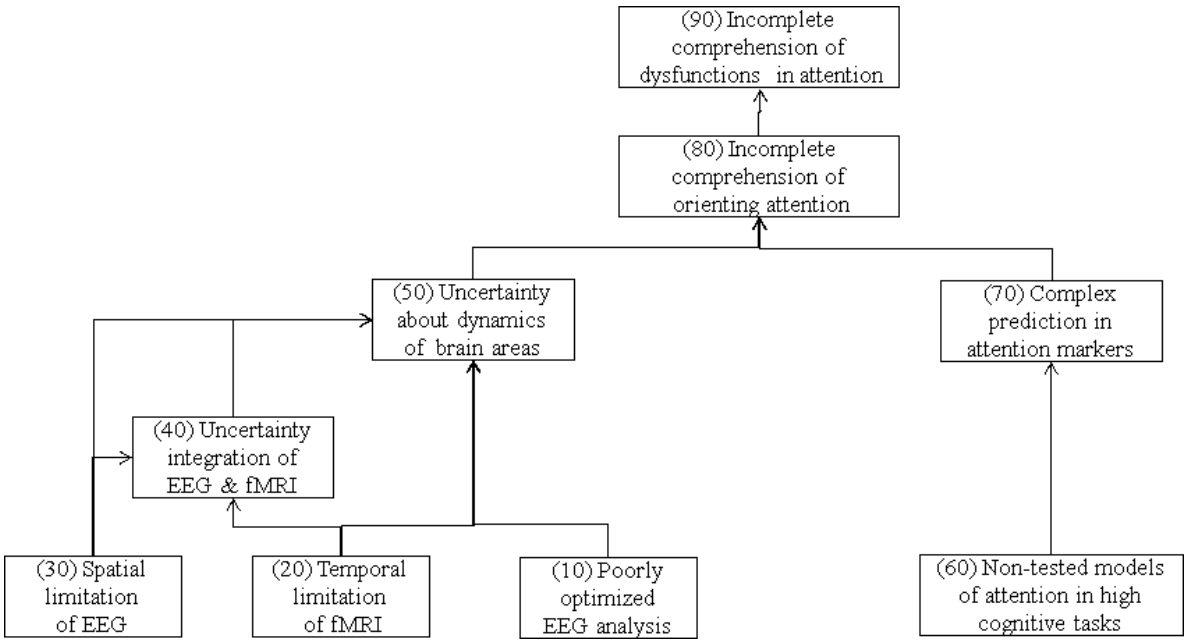


Figure 4 Tree of problems associated with solving the orienting attention mechanisms examined in this dissertation. The problems in which our general aims are involved consist of a number of technological limitation and a scarcity of systematic testing of cognitive models.

1.4 Aims.

A central assumption of this research is that orienting to novel distractors involves the activation of the ventral right lateralised stimulus-driven attention network followed by orienting of the dorsal bilateral goal-driven attention network to a novel or behaviourally relevant stimulus (Corbetta et al., 2002, 2008). An important alternative, historical hypothesis is that the goal-driven network initiates orienting prior to the stimulus-driven network and that this is consistent with the stimulus-driven network being better considered as a system involved in context updating (Donchin, 1981).

The main hypothesis of this research is that a sequence of stimuli with identifiable variations in properties (*e.g.* temporal probability, frequency, duration, amplitude) will cause a predictable pattern of changes in neural signals and that part of this will be detectable at the scalp.

In this way, it is possible to hypothesize that including stimulus sequence properties as regressors as well as the categorical predictors will improve the statistical power of studies of attention function. This hypothesis was explored from 3 points of view: Oddball paradigm with several conditions, Oddball paradigm with brain sources temporally and spatially distinguished, and Oddball paradigm with different temporal properties.

1.5 Introduction to the Following Chapters

This work sought a comprehensive examination of the dynamic of orienting responses within an auditory focused attention system(s) in the human brain. To achieve this, we have used an auditory oddball parity decision task in three ways. First, in Chapter 2, we have used a novel distractor in the cue, target or simultaneous with the target as a paradigm in EEG experiments comparing between controls and schizophrenics. Further, in Chapter 3 we have used the paradigm without cues and use the advantage of temporal resolution of electroencephalography (EEG) and spatial resolution of functional magnetic resonance imaging (fMRI). By combining both, the aim of the desing in Chapter 4 is to improve the comprehension of the dynamics of the brain areas involved in orienting attention. Finally, in Chapter 5, we have designed, run and analysed EEG experiments exploring time and novel sound features in novel distractors instead of the cue to induce switching between alerting and orienting and test attention theories.

2 ATTENTION AND DISTRACTION IN CONTROLS AND SCHIZOPHRENIC PATIENTS: AN ANALYSIS OF STIMULUS PROPERTIES AND STIMULUS PROBABILITY AS PREDICTORS OF P300 ERP AMPLITUDE VARIABILITY

2.1 Introduction

The analyses described in this chapter were carried out using an existing set of data. The original aim of this study was to test the hypothesis that cognitive impairment in medicated schizophrenic patients is partially the result of impairments of attention control (Laurens, Kiehl, Elton, Ngan, & Liddle, 2005) in the form of reduced efficiency of goal-driven control mechanisms (GDN) and a possible enhancement of sensitivity of stimulus-driven control mechanisms (SDN) to distractor stimuli (Corbetta & Shulman, 2002). The task consisted of a centrally presented warning tone (S1) followed 300 ms later by a centrally presented number between 2 and 9 (S2). Participants had to indicate with a button press whether the number was odd or even. The purpose of the warning tone (S1) was to provide an alerting cue that could be replaced with a novel stimulus to induce an orienting response (and associated P3a) and slow the subsequent responses in the number decision task. In other trials a novel sound either replaced the number (S2) or occurred simultaneously with the number. This resulted in a right lateralised P3 response appearing, which was hypothesised to be a marker of activation of the stimulus-driven system but not the goal-driven system. In these cases a central P3a response was not observed and this was interpreted as consistent with the view that if the GDN is engaged with a stimulus it tends to suppress responses from the stimulus driven system that might lead to orienting and the production of a central P3a response. Novel distractors were always presented laterally. Initial analysis suggested that the P3a marking orienting (S1) was smaller in schizophrenics, consistent with many previous findings whereas the P3 associated with (S2) distractors was larger, suggesting increased activation of the stimulus driven system (Potter et al., 2008). Therefore, Potter and colleagues

aimed to use carefully timed novel distractors to attempt to dissociate activation of the goal-driven (GDN) attention network from activation of the stimulus-driven attention network (SDN) using ERP markers. Therefore, the aim of this research, by reanalysing the data, was to use single-trial analysis techniques to attempt to disentangle the effects of variation in stimulus probabilities from group differences in ERP markers of attention control.

Before describing in detail the reanalysis of the data, the relevant background literature will be briefly reviewed. The finding that a cue stimulus preceding a goal stimulus by a fixed interval speeds up response time is one of the oldest phenomena reported in psychology (*e.g.*, Wundt, 1880 cited in Hackley, 2009). The effect also works across modalities (Bertelson, 1967; Bertelson., & Tisseyre, 1968; Davis & Green, 1969). Studies have shown this effect in blocked designs, where a cue always announces the upcoming presentation of a target and precedes it by a fixed amount of time (*e.g.*, Näätänen, 1970; Woodrow, 1914). This type of non-spatial cue warns the participant of the upcoming target. Whether the cue results in alerting or alerting and orienting of attention to a particular point in time is not clear (Posner & Rothbart, 2007; Hackley, 2009). Moreover, in auditory-visual crossmodal task the changes of reaction times were interpreted as distraction in attention tasks when the source of auditory signal (Corral & Escera, 2008). As Parmentier and colleagues have pointed out, one needs to note that orienting paradigms were not done in mixed blocks where targets do not always follow warnings or only do so after a temporal interval varying from trial to trial (Parmentier, Elsley & Ljungberg, 2010). Parmentier and colleagues hypothesized that an orienting response to a novel stimulus may be influenced by the informational content of the sound in a particular context. They explored this hypothesis in a three experiment between-subject study: a) In the first 'Informative' experiment, standard (p = 0.8) and deviant (p = 0.2) tones always predicted a visual digit 250 ms later. b) In the second 'Uninformative' experiment the tones predicted a visual digit at 150, 250 or 350 ms only 50% of the time. c) In the

'Informative Deviant' experiment the (p = 0.8) standard tones predicted a visual digit 50% of the time and the (p = 0.2) deviants predicted a visual digit 100% of the time. In each case the digit had to be categorised as odd or even. They found in the 'Informative' condition that when the deviant stimulus predicted targets at the same rate as standard stimuli then RTs were slower to deviants. In the second 'Uninformative' experiment, in which standards and deviants did not differentially predict the timing of visual digits, they found no difference between the RTs. In the final experiment in which standard stimuli only predicted visual digits 50% of the time but novel stimuli predicted visual digits 100% of the time they found that deviants now improved reaction times. Therefore, the results suggest that distraction is not present for deviant sounds with low information content, and also that deviant sounds can improve the performance when these deviants carry additional information not contained in the standard stimuli (Parmentier, Elsley & Ljungberg, 2010).

Novel events are believed to be responsible for a pattern of responses marked by specific brain ERP waves: first, the automatic novelty-detection response or MisMatch Negativity (MMN; *e.g.*, Näätänen et al., 1978; Näätänen & Winkler, 1999; Picton, Alain, Otten, Ritter, & Achim, 2000); second, the involuntary orientation response (P3a; *e.g.*, Näätänen & Teder, 1991; Friedman, Cycowicz, & Gaeta, 2001; Grillon, Courchesne, Ameli, Geyer, & Braff, 1991; Woods, 1992); and third, when the participant is engaged in a task, the Re-Orienting Negativity (RON; *e.g.*, Berti, Roeber, & Schröger, 2004; Berti & Schröger, 2001; Schröger & Wolff, 1998a). These unexpected novel sounds produce measurable behavioural effects such as longer reaction times and a distinctive pattern of ERP deflections that include the MMN (*e.g.*, Schröger, 1996), the P3a (e.g. Woodward, Brown, Marsh, & Dawson, 1991) and the RON (Schröger and Wolff, 1998a).

The oddball task is one of the most reported paradigms in the literature. In the oddball task, when the Inter-Stimulus Interval (ISI) is constant, the longer the non-target sequence length, the greater the P300 amplitude will be to a target stimulus (Gonsalvez, Gordon, Grayson, Barry, Lazzaro, & Bahramali, 1999). Moreover, in an extensive review of P300 research, Polich stated that a novel or deviant distractor produces a larger P300 response. These P300 changes are interpreted as possible markers of attention activation and subsequent alterations of the content of short-term and long-term memory (Polich, 2007).

There is a strong P3a response at a low novel probability of 25% (classical Posner probability) or at lower probability, such as 15% (*e.g.* Potter, Bassett, Jory & Barrett, 2001) and the magnitude of the response is influenced by the task relevance of novel stimuli even at local probabilities of 50% (Parmentier, Elsley & Ljungberg, 2010).

Early studies of visual and auditory P300 suggest that the auditory P300 is more sensitive to schizophrenia than the visual P300 (Ford, 1999; Jeon & Polich, 2003), and that the goal-driven attention processes reflected by target P3b may be particularly sensitive to higher-order cognitive deficits in schizophrenia relative to the stimulus-driven processes that may contribute to the P3a signal. P300 (P3b), has been proposed as a biological marker in schizophrenic patients because the P3b amplitude was reduced (McCarley, Faux, Shenton, Nestor, & Holinger, 1991). The model of P300 wave generators suggested by Polich proposed the activation of anterior cingulate structures for P3a and activation of temporo-parietal structures for P3b (Polich, 2007). Mathalon and colleagues aimed to have a more complete framework in their study of the sensitivity of the P3b and P3a in auditory and visual oddball paradigms to the effects of schizophrenia. A direct comparison of visual and auditory P3a and P3b failed to support the suggestion of differential sensitivity in schizophrenia. Their results suggest that the P300 is reduced and delayed in schizophrenia to the same degree, in

both sensory modalities and that the same attention system is engaged (Mathalon et al., 2010).

In an attempt to draw a more direct comparison between ERP markers and cognition, Kirihara and colleagues compared healthy subjects (n=58) and schizophrenic patients (n=60) in a three-tone oddball task (40 target stimuli and 200 standard stimuli and 40 novel stimuli) and calculated correlations between P300 amplitude (P3a at Cz; P3b at Pz) and scores in the Comprehension Index of Positive Thought Disorder (CIPTD), and found a significant correlation of P3b (r = -.322, p = .012) and non-significant correlation of P3a (r = .088, p = .609) with a mean peak P3a at Fz of 11.15 uV +/- 4.4 uV in controls and 8.75 uV +/- 5.7 uV in schizophrenics. Both correlation results are supported by the idea that the frontal lobe activity generates P3a for attention processing while P3b is strongly linked to memory by the measure of CIPTD (Kirihara et al., 2009). It also allows the visualisation of differences in MMN responses around 100 ms between both groups.

There are several studies that explored the possibility of different activations in MMN in control and patients with cognitive impairment. For example, for deviant tones in an auditory task, the MMN was more prominent at frontal and right temporo-parietal electrodes in control participants and more frontal or frontal and central in medicated and non-medicated Parkinson disease, respectively (Solís-Vivanco et al., 2011). In schizophrenic patients, Näätänen and Kähkönen reviewed several MMN articles and they found that MMN attenuation is in the temporal lobe for positive disease and is in the frontal lobe for switching attention (see review by Näätänen & Kähkönen, 2009).

Many of the paradigms manage probability using two or three conditions rather than those two conditions in the original Posner's experiments (Posner, Snyder & Davidson, 1980). The paradigm that we decided to explore has four conditions, therefore not only we can do more

analysis between conditions but also we can study more effects of local probability in the switching of attention. The aim of the reanalysis of this data was to explore the effect of local probability on single trial P3a variance when a novel stimulus replaces the standard tone in the warning signal S1 and its link with MMN in the different conditions when the distractor is presented at different times at low local probability. Subsequently, the main analysis was to employ single trial analysis methods to determine whether the originally observed P3 effects can be enhanced by controlling for the effects of variables such as local probability as well as differences in the amplitude, duration or frequency content of the sound stimuli used in the task.

On the basis of the literature reviewed here it was hypothesized (H):

H1: Based on previous results regarding P3a amplitude in controls (Gonsalvez et al., 1999, 2002) and in schizophrenic patients (Kirihara, 2009), there will be a decrease in amplitude of P3a over time to novel stimuli (that replace the tone cue) as task duration (familiarity) increases that this will be greater in the control than in the schizophrenic participants.

H2: Based on previous results regarding P3a amplitude (Gonsalvez et al., 1999, 2002) and changes in reaction time due to informational content (Parmentier et al., 2010), the amplitude of P3a to novel stimuli (that replace the tone cue) will be systematically related to the local probability of novel stimuli, as well as to a lesser degree fluctuations of frequency, amplitude and duration stimuli of immediately preceding cue, goal or novel stimuli.

H3: Based on previous findings on schizophrenia patients with regard to P300 amplitude (McCarley et al., 1991; Kirihara et al., 2009; Mathalon et al., 2010) and MMN modulatioation (Näätänen & Kähkönen, 2009), there will be a significant negative correlation between P3a amplitude on the current trial and the MMN on the subsequent trial. The

rationale being that when the P3a to a novel stimulus is smaller, suggesting impaired context updating, then the ERP in the next trial shall be prone to produce a larger MMN to the next standard stimulus.

2.2 Methods

Participants.

Thirty four adults participated in this study: twenty-one healthy subjects (mean age: 36.1 ± 11.3 years; range 22–63 years) and thirteen schizophrenic individuals (mean age: 41.1 ± 11.1 years; range 22–60 years). All subjects were free from any history of auditory deficits or other known neurological illness. All participants consented to participate in the study. One healthy participant and one schizophrenic participant were excluded because there were too few usable segments of EEG data as the result of recording artifacts (<100 segments), leaving 20 healthy (20 right handed) subjects and 12 schizophrenic (12 right handed) subjects.

Experiment Design

Subjects were asked to perform an odd/even number decision while their scalp EEG was recorded. The paradigm was composed of 600 trials, with trials chosen pseudo-randomly from one of four different conditions. Each trial consisted of a pair of sound stimuli. The parameters of the stimuli are given in Table 1. Participants were asked to respond by pressing a button as quickly as possible without sacrificing accuracy. One button was pressed when the number was odd and another button was pressed when the number was even. Hand preference of response was counter-balanced across subjects. The Inter-Trial Interval (ITI) was 2300 ms. The task was presented in 5 separate blocks (120 trials each) with each of the four conditions presented in random order. Stimulus sequence was the same across all participants.

Table 1

Stimuli combinations for the experiment 1.

Stimuli name	Number of presentations	Code Processed	Stimuli				
			S1		SOA		S2
			Type	*Time*		*Type*	*Time*
Standard goal stimuli	450	TG	Tone	50 ms	300 ms	Number	300 ms
Novel only	50	TN	Tone	50 ms	300 ms	Novel	200 ms
Simultaneous novel and goal	50	TNG	Tone	50 ms	300 ms	Number + Novel	300 ms
Novel Preceding the goal	50	NG	Preceding novel	100 ms	300 ms	Number	300 ms

SOA: Stimulus-onset asynchrony

Stimuli

The sound stimuli were presented using Beyer Dynamic Headphones (DT 770) headphones at 75 dB sound pressure level. Sounds files were stereo with 16 bit resolution and 22050 Hz sampling rate.

For the standard goal stimuli condition (TG), the first stimuli of each pairs (S1) were 50 ms duration pure tones with 10 ms rise/fall times followed by a number sound (S2) of 300 ms duration.

For the novel only condition (TN), S1 were pure tones as in the TG condition, followed by a novel sound. These sounds were 100 ms duration.

For the simultaneous novel and goal condition (TNG), S1 were pure tones as in the TG condition, followed by a number sound of 300 ms duration and a simultaneous laterally presented novel sound of 100 ms duration. These sounds were 300 ms duration.

For the novel preceding the goal condition (NG), the first stimulus of each pair (S1) was either white noise (26 stimuli, 100 ms duration) or samples of environmental sounds (24 stimuli, 100 ms duration). An in-house Matlab script (detailed results of these calculations are not presented here) was used to calculate the following sound properties (see below). A correlation matrix was next computed to assess how the properties of the sounds related to each other (bootstrapped correlations with False discovery rate correction of p values p=.05). From these results, an exploratory analysis to determine which of these sound properties modulated the P300 was conducted.

14 parameters were obtained from each pair of sounds S1 and S2:

R(n,1), R(n,2) and R(n,3): Fundamental frequency of S1, S2 and S1-S2 (*i.e.* R(n,3) = R(n,2) - R(n,1).

R(n,4), R(n,5) and R(n,6): Sound durations of S1, S2 and S1-S2 (*i.e.* R(n,6) = R(n,5) - R(n,4).

R(n,7): Average difference in the long term average spectrum (LTAS) between S1 and S2.

R(n,8): Normalized mutual information in frequency between S1 and S2 .

R(n,9), R(n,10) and R(n,11): Mean amplitude in time of S1, S2 and S1-S2 (*i.e.* R(n,11) = R(n,10) - R(n,9).

R(n,12), R(n,13) and R(n,14): Root mean square (RMS) in time of S1, S2 and S1-S2 (*i.e.* R(n,14) = R(n,13) - R(n,12).

More parameters were next obtained in trials involving lateralised distractor sounds by combining previous measures of the left part of the sound and right part of the sound with train sequence, task probability and preceding novel sequence probability:

Current S1 with previous S2, *i.e.* S1(k) and S2(k-1)

Current S1 with previous S1, *i.e.* S1(k) and S1(k-1)

Current S1 with previous novel on one of S1 or S2, i.e. S1(k) and novel(S1vS2, k-1).

Current S1 novel with previous preceding novel on S1, *i.e.* S1(k) and novel(S1(k-1))

There are 14 parameters, 4 are exclusively for S1 which in the following results was the current cue or preceding novel and was compared with the other 5 sounds (current goal, previous goal, previous tone/preceding novel, previous novel on one of S1 or S2 and previous preceding novel) leaving the other 10 parameters per comparison in the left and right side. This gave an outcome of 108 parameters: 54 in the left and 54 in the right side. The parameters of the sound measures in the right ear are given in table 2.

The matrix correlation between these 54 parameters per side was computed with 500 resamples following a bootstrap correlation analysis and is showed in every condition 1 (TG), 2 (TN), 3 (TNG), 4 (NG).

EEG Recording.

Participants were seated in an armchair in a light and sound-attenuated room, and the keyboard was near to their hands. EEG data were recorded with a BioSemiActiveTwo 32-channel EEG (BioSemi Inc., Amsterdam, The Netherlands) acquisition system working with BioSemiActiView software (CortechSolutions). Amplified signals were digitized at 2500 Hz with a 16-bit resolution. All electrode impedances were < 20 kΩ. Data were band-pass filtered between 0.2–500 Hz during data acquisition. Eye movements and blinks were recorded with two horizontal electrodes in the outer canthus of both eyes (HEOG) and two vertical electrodes in the infraorbital and supraorbital regions of the left eye (VEOG).

Table 2

Sound properties explored on the events of the experiment between control participants and schizophrenic patients.

Stimuli name	Stimulus property used for the calculi	Property seek in
Freq(S1R)	Frequency of S1	Current event
Dura(S1R)	Duration of S1	
Rms(S1R)	Root mean square (RMS) in time of S1	
Std(S1R)	Standard deviation of S1	
Freq(S2,R)	Frequency of S2	
Freq(S1R-S2,R)	Frequency of S1 - frequency of S2	
Dura(S2,R)	Duration of S2	
Dura(S1R-S2,R)	Duration of S1 - duration of S2	
Ltas(S1R,S2,R)	Average difference in the long term average spectrum between S1 and S2	
Entr(S1R,S2,R)	Normalized mutual information in frequency between S1 and S2	
Rms(S2,R)	Root mean square (RMS) in time of S2	
Std(S2,R)	Standard deviation of S2	
Rms(S1R-S2,R)	Root mean square in time of S1 - Root mean square in time of S2	
Std(S1R-S2,R)	Standard deviation of S1 - standard deviation of S2	
Freq(S2(t-1))	Frequency of the previous S2	Previous event (previous S2)
Freq(S1R-S2(t-1))	Frequency of S1 - frequency of the previous S2	
Dura(S2(t-1))	Duration of the previous S2	
Dura(S1R-S2(t-1))	Duration of S1 - duration of the previous S2	
Ltas(S1R,S2(t-1))	Average difference in the long term average spectrum between S1 and S2	
Entr(S1R,S2(t-1))	Normalized mutual information in frequency between S1 and the previous S2	
Rms(S2(t-1))	Root mean square of the previous S2	
Std(S2(t-1))	Standard deviation of the previous S2	
Rms(S1R-S2(t-1))	Root mean square in time of S1 - Root mean square in time of the previous S2	
Std(S1R-S2(t-1))	Standard deviation of S1 - standard deviation of the previous S2	
Freq(S1(t-1))	Frequency of the previous S1	Previous event (previous S1)
Freq(S1R-S1(t-1))	Frequency of S1 - frequency of the previous S1	
Dura(S1(t-1))	Duration of the previous S1	
Dura(S1R-S1(t-1))	Duration of S1 - duration of the previous S1	
Ltas(S1R,S1(t-1))	Average difference in the long term average spectrum between S1 and the previous S1	
Entr(S1R,S1(t-1))	Normalized mutual information in frequency between S1 and the previous S1	
Rms(S1(t-1))	Root mean square of the previous S1	
Std(S1(t-1))	Standard deviation of the previous S1	
Rms(S1R-S1(t-1))	Root mean square in time of S1 - Root mean square in time of the previous S1	
Std(S1R-S1(t-1))	Standard deviation of S1 - standard deviation of the previous S1	
Freq(Nov(t-1)R)	Frequency of the previous novel, either on S1 or on S2	Previous novel, either on S1 or on S2
Freq(S1R-Nov(t-1)R)	Frequency of S1 - frequency of the previous novel, either on S1 or on S2	
Dura(Nov(t-1)R)	Duration of the previous novel, either on S1 or on S2	
Dura(S1R-Nov(t-1)R	Duration of S1 - duration of the previous novel, either on S1 or on S2	
Ltas(S1R,Nov(t-1)R)	Average difference in the long term average spectrum between S1 and the previous novel, either on S1 or on S2	
Entr(S1R,Nov(t-1)R)	Normalized mutual information in frequency between S1 and the previous novel, either on S1 or on S2	
Rms(Nov(t-1)R)	Root mean square of the previous novel, either on S1 or on S2	
Std(Nov(t-1)R)	Standard deviation of the previous novel, either on S1 or on S2	
Rms(S1R-Nov(t-1)R)	Root mean square in time of S1 - Root mean square in time of the previous novel, either on S1 or on S2	
Std(S1R-Nov(t-1)R)	Standard deviation of S1 - standard deviation of the previous novel, either on S1 or on S2	
Freq(S1(PN)R)	Frequency of the previous novel on S1	Previous novel on S1
Freq(S1R-S1(PN)R)	Frequency of S1 - frequency of the previous novel on S1	
Dura(S1(PN)R)	Duration of the previous novel on S1	
Dura(S1R-S1(PN)R)	Duration of S1 - duration of the previous novel on S1	
Ltas(S1R,S1(PN)R)	Average difference in the long term average spectrum between S1 and the previous novel on S1	
Entr(S1R,S1(PN)R)	Normalized mutual information in frequency between S1 and the previous novel on S1	
Rms(S1(PN)R)	Root mean square of the previous novel on S1	
Std(S1(PN)R)	Standard deviation of the previous novel on S1	
Rms(S1R-S1(PN)R)	Root mean square in time of S1 - Root mean square in time of the previous novel on S1	
Std(S1R-S1(PN)R)	Standard deviation of S1 - standard deviation of the previous novel on S1	

Sound properties for right ear are shown (R: Right Ear), codes are similar for the left ear, changing R per L (L: Left Ear).

Data Analysis.

Goal conditions in this study are the standard goal stimuli (TG), the simultaneous novel and goal (TNG), and the novel preceding the goal (NG). Behavioural data in groups, controls and schizophrenic patients, with these three factors were first explored through Matlab functions to plot the mean and variance for both groups in each condition as within-group factor.

The reaction times were analysed using a 2 x 3 analysis of variance (ANOVA) using SPSS19 with groups as the between-subject factor and with goal conditions as the within-group factors.

Given the variability of the behavioural responses across participants, a time series analysis of individual condition effects was done with a running average reaction time for each participant. The running average reaction time (RT) of the standard Goal stimulus, the simultaneous Novel and Goal conditions were explored using in-house Matlab functions in which the standard Goal stimulus RT was subtracted from the simultaneous Novel and Goal conditions. The running average RT of the standard goal stimulus was then subtracted from the simultaneous goal and novel conditions. Average and standard deviation calculation of reaction times was calculated by taking, as the centre, the central trial plus/minus 75 trials (condition TG), 15 (condition TNG) and 15 (condition NG) across the whole possible range of accurate answered trials. Because of this the trial axis does not start from 0 and finish at 400. This calculation of the effect of each condition on RT over time used 151 trials of (condition TG), 15 of (condition TNG) and 15 of (condition NG). In addition, measures of the difference between both TNG and NG with the TG were computed, through an interpolation of the values.

EEG pre-processing was conducted first through Polyrex (Polygraphic Recording Data Exchange – PolyRex, Kayser, 2003). Analyzer software (Brain Vision, LLC) was then used to downsample the EEG data from 2500 Hz to 128 Hz. After EEG-data were referenced to the mastoid, they were analyzed using EEGLAB (Delorme & Makeig, 2004) and Matlab in-house scripts. Eye-movements and artifacts were removed through an independent components analysis (ICA). Data were then filtered with a high-pass at 0.75 Hz and epoched from 300 ms before stimulus onset to 600 ms after stimulus onset. A baseline correction was then applied. The epochs were then checked for trials with excessive peak-to-peak deflections, amplifier clipping, or other artifacts.

Three approaches were taken to the analysis of the EEG data. In the first approach, to investigate the relationship between sound properties and the P300, single trial across-subjects averages were next computed for the 20 healthy participants and the peak amplitude between 350 and 450 ms of the Novel-Goal condition was taken as a measure of the P3a orienting response to the novel stimulus preceding the number decision. Correlations were next computed between amplitudes and the sounds properties (600 bootstrap percentile correlations) and a FDR correction for multiple testing applied (p<.05)

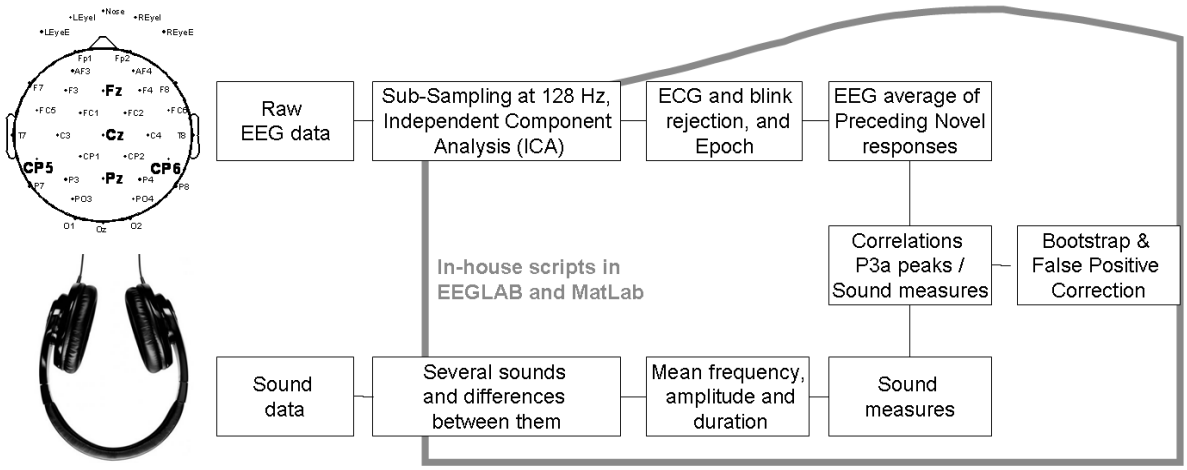


Figure 5 Block diagram of data processing in the first study.

P3a amplitude measures from the EEG average in 20 controls and either sound properties or probabilities were then correlated using a bootstrap method (600 iterations) and a further correction of false positive of $p < .05$.

The purpose of the second analysis was to explore sources of variability of P3a deflection associated with the context of the immediately preceding trial. Seven conditions were identified and the ERP deflections to the second trial were computed for each subject. These were: standard goal followed by the standard (TG.TG), standard goal followed by the novel only (TG.TN), standard goal followed by the preceding novel (TG.NG), standard goal followed by the simultaneous novel and goal (TG.TNG), simultaneous novel and goal followed by the standard goal (TNG.TG), novel target followed by the standard goal (TN.TG) and preceding novel followed by the standard goal (NG.TG).

The ERP generated by the TG.TG condition was then subtracted from each of the other conditions to separate out the effects of the novel stimuli from the basic response to the number decision task. Therefore, within groups t-tests between each condition and the standard was run ($p<.001$) for significant differences at each time and for each channel.

In the third approach, using sounds properties that influenced the P300, all the conditions were next analysed using LIMO EEG (Pernet et al., 2011). For each subject, an ANCOVA model was used: the 4 conditions plus 2 covariates coding for sounds: LTAS and RMS between the current preceding novel (NG) trial and the previous NG trial, using a simple hierarchical model of the EEG data with β_i as the constant and S_i y A_{j-8} as the categorical and the continuos regresors following the equation:

$$EEG = \beta 0 + \sum_{i=1}^{8} \beta_i S_i + \sum_{j=9}^{10} \beta_j A_{j-8} + Error$$

Parameters (β-values) were evaluated at every electrode and time point autonomously, yielding a lattice of 32 (electrodes) * 102 (time focuses, from −300 ms to 492 ms in 7.82 ms steps) for each regressor. Comparative electrode*time point frameworks were processed for R2, F and p-values for both the linear models and for each regressor (partial F-values).

At the group level, Figure *6* shows that a repeated measure ANOVA was conducted on the parameters computed for each condition. Because sounds properties that influenced the P300 were regressed out for each subject / trial, differences between conditions can only reflect differences due to novelty and not differences between stimuli in the different conditions. The purpose of this analysis was to explore sources of variability of P3a deflection associated with attention orienting.

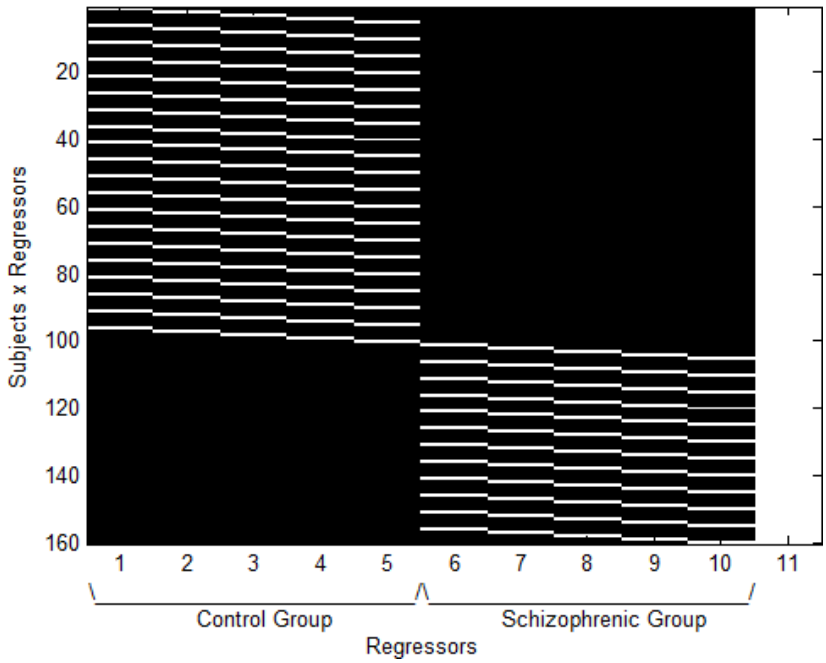


Figure 6 Design matrix of the second level ANOVA model considering 4 conditions and 1 covariate in the first level analysis and taking these ones as 5 regressors in the second level analysis to make comparison between Control and Schizophrenic patients groups.

2.3 Results

2.3.1 Behavioural Results

Reaction times for the standard goal stimuli (TG), novel preceding the goal (NG), novel target (TN) and simultaneous novel and goal (TNG) were analysed. *Figure 7* shows the mean reaction times in each condition in control and schizophrenic patients.

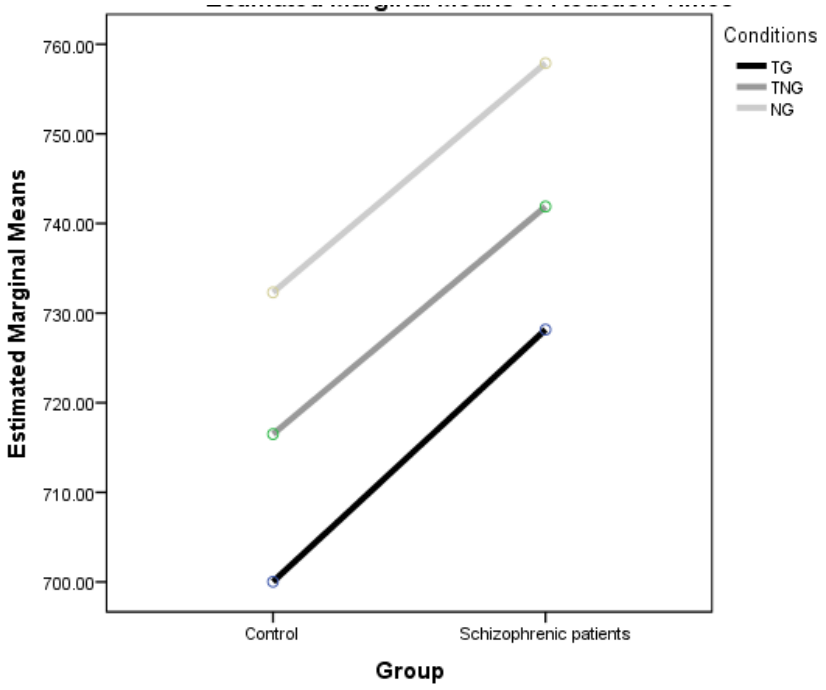


Figure 7 Effect of preceding (NG) and simultaneous (TNG) distractors on number parity decisions compared to simple number decision task (TG).

Overall, participants performed well (*94% accuracy of goal trials*). The Group ANOVA of reaction times yielded significant main effects of group ($F(1,30)=19.68$, $p<.001$, $\eta =.001$), schizophrenic patients showed delayed reaction times. The Conditions ANOVA of reaction times yielded significant main effects ($F(2,60)=13.28$, $p<.001$, $\eta = .002$). This was due to differences between NG and either TG (difference of 30.96 ms at $p < .001$) or TNG (difference of 27.94 ms at $p = .001$) found in a *post hoc* test using Fisher's least significant difference (LSD). In addition, there were no differences between TG and the other two goal conditions. Although significant differences were found, effect of size (η) was small, *i.e.* less

than 0.01 (Cohen, 1992) between groups (η = .001) and between conditions inside a group (η = .002). There was no significant interaction between Group and Condition ($F(2,60)=.039$, p= .962, $\eta<.001$).

To explore distraction effects over the duration of the experiment, running averages of Reaction time (RT) in 20 control participants and 12 schizophrenic patients for conditions TG (coloured in black), TNG (coloured in gray) and NG (coloured in light gray) were calculated and three participants in control group are illustrated in *Figure 8*. Solid lines in the upper plots are the means for each condition (black for standard goal stimuli, gray for the simultaneous novel and goal, and light gray for novel preceding the goal). In the bottom plots the difference of the reaction times (RT) between the standard target minus, the simultaneous novel and goal and minus the novel preceding the goal are plotted.

From the results in the control participants the reaction times for the novel preceding the goal (NG) are slower (suggesting orienting) in: P27, P30 (also for TNG), P31, P32 (also for TNG), P35 (also for TNG), P36 (also for TNG), P37 (also for TNG), P38 (also for TNG), P39 (also for TNG), P41, P44, P55, P57, P59, P60, faster (suggesting alerting) in: P51, P56 and similar in: P33, P36, P49, P50. From the results in the schizophrenic patients the reaction times for the novel preceding the goal (NG) are: slower (suggesting orienting) in: P14 (also for TNG), P15 (also for TNG), P17, P18 (also for TNG), P19, P23, P24 (also for TNG), P28, P29 but faster (suggesting alerting) in: P21& P22. This suggests important individual differences in the way that participants reacted to these stimuli and were potentially distracted by them.

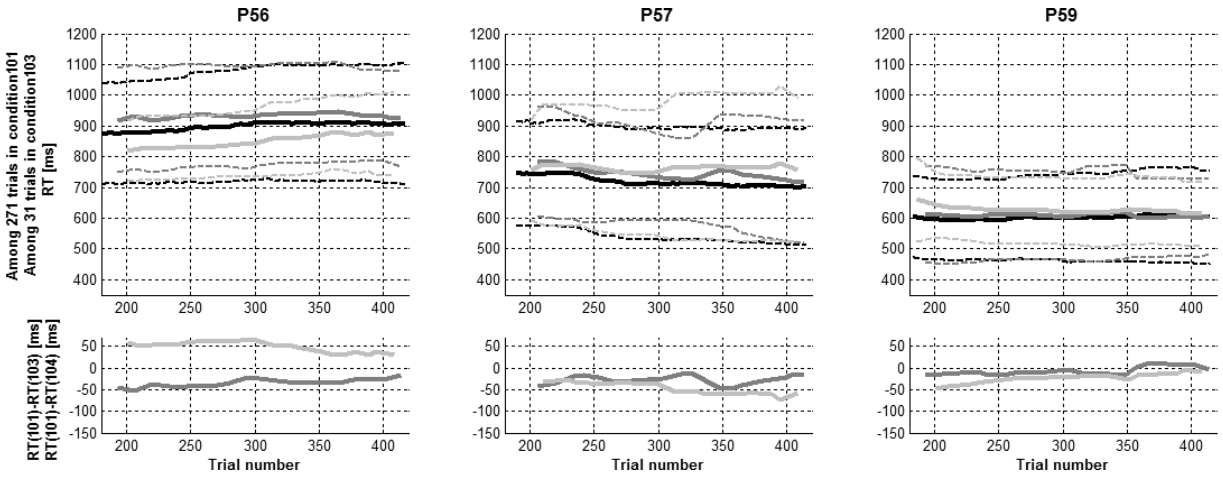


Figure 8 Running average of Reaction Time (RT) for conditions TG (coloured in black) and TNG (coloured in gray) and condition NG (coloured in light gray) in three of the 20 control participants. Solid lines in the upper plots are the means at every condition (black for standard target condition and gray for noisy target). In the bottom plots the difference of the reaction times (RT) between TG and TNG and TG and NG are shown.

Overall, the small effect size in the differences in RT in the 2 x 3 ANOVA may be explained by the individual differences in pattern of the running average reaction times in the different conditions. Some individuals clearly show distraction effects while others do not.

2.3.2 EEG results.

Prior to the detailed analyses, the EEG data were averaged by condition to determine the latency ranges that would be best for estimating responses in single trial analyses. The grand average ERP waveforms associated with standard goal stimuli (TG), novel only (TN), simultaneous novel and goal (TNG) and novel preceding the goal (NG) conditions for the schizophrenic group and control group are shown in *Figure 9* and *Figure 10*.

The waveforms are characterized by a positive peak between 200 ms and 250 ms after the first stimulus for conditions TG, TN, and TNG and 300 ms and 450 ms for condition NG.

Therefore in the NG condition, the P300 response to the preceding novel stimuli was estimated on a trial by trial basis as the maximum peak between 250 ms and 450 ms. In *Figure 9* the across subject averaging for each trial in Pz electrode and weighted for Pz electrode, there is shown in colour the fluctuations trial by trial for each condition: TG, NG, TN and TNG respectively. From *Figure 9* it is clear that NG is changing positively in the different trial averaging in the [250, 450] ms range clearly along the experiment, while TG, TN and TNG are not (see dashed line). Figure 11 also shown the statistical t-test difference between condition TG and each one of conditions NG, TN and TNG (p = .001) and a window time of 187.5 ms. In both groups there is a difference between NG and TG conditions in the electrode Pz. In the schizophrenic patients, there is an additional difference around 300 ms between TN and TG conditions.

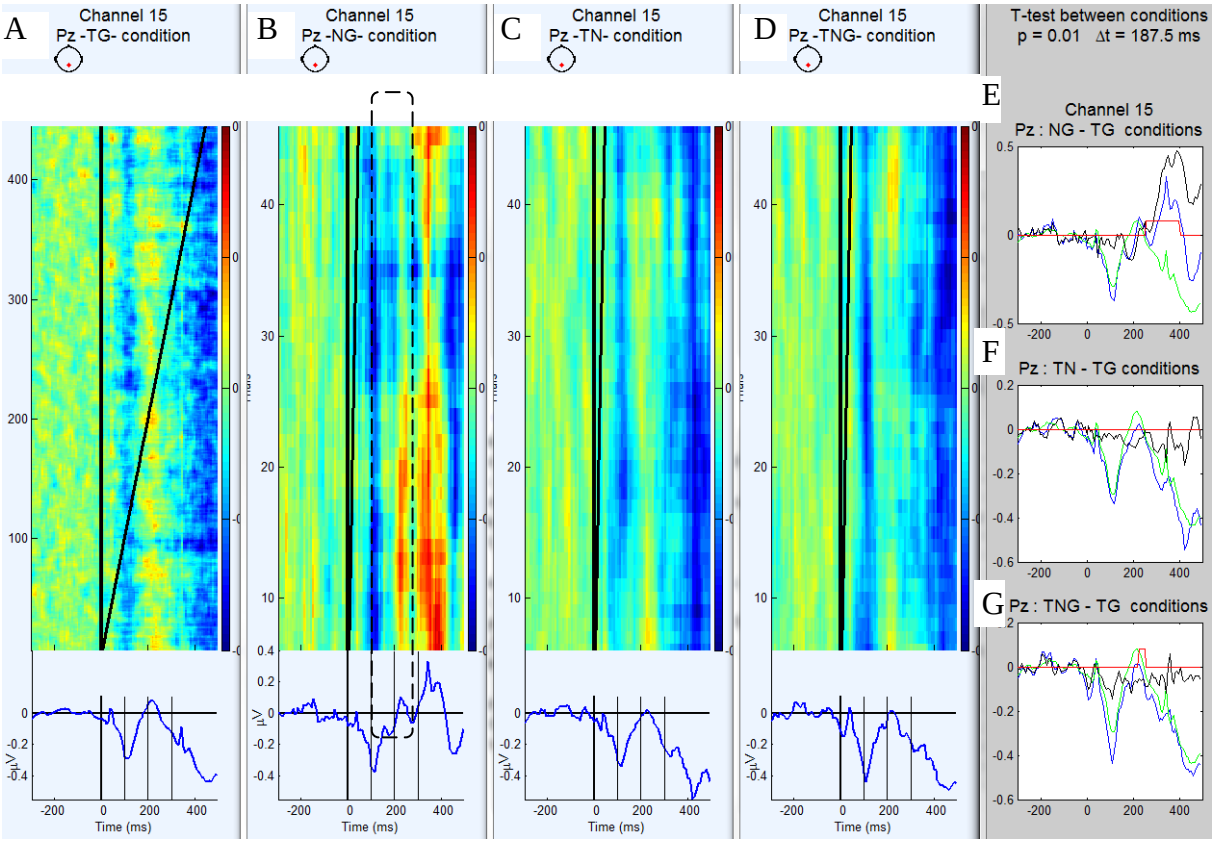


Figure 9 (A-D) Grand average ERP waveforms and trial by trial voltage plots at Pz electrode in 20 control participants in the standard goal (TG), novel preceding goal (NG), novel target

(TN) and simultaneous novel and goal (TNG) conditions. (E-G) Waveforms generated by subtraction (in black) of novel conditions from control condition (TG in green) and corresponding t-values for successive time bins of 187.5 ms.

Both groups exhibit a significant P3 response to the novel stimuli that replace tone cue (in NG-TG condition) and this response is larger in the control group than the schizophrenic group (p = 0.01). This is consistent with previous research that suggests a reduction in the effectiveness of cognitive processes attributed to P300 in Schizophrenia (*e.g.* Kirihara et al., 2009; Özgürdat et al., 2008).

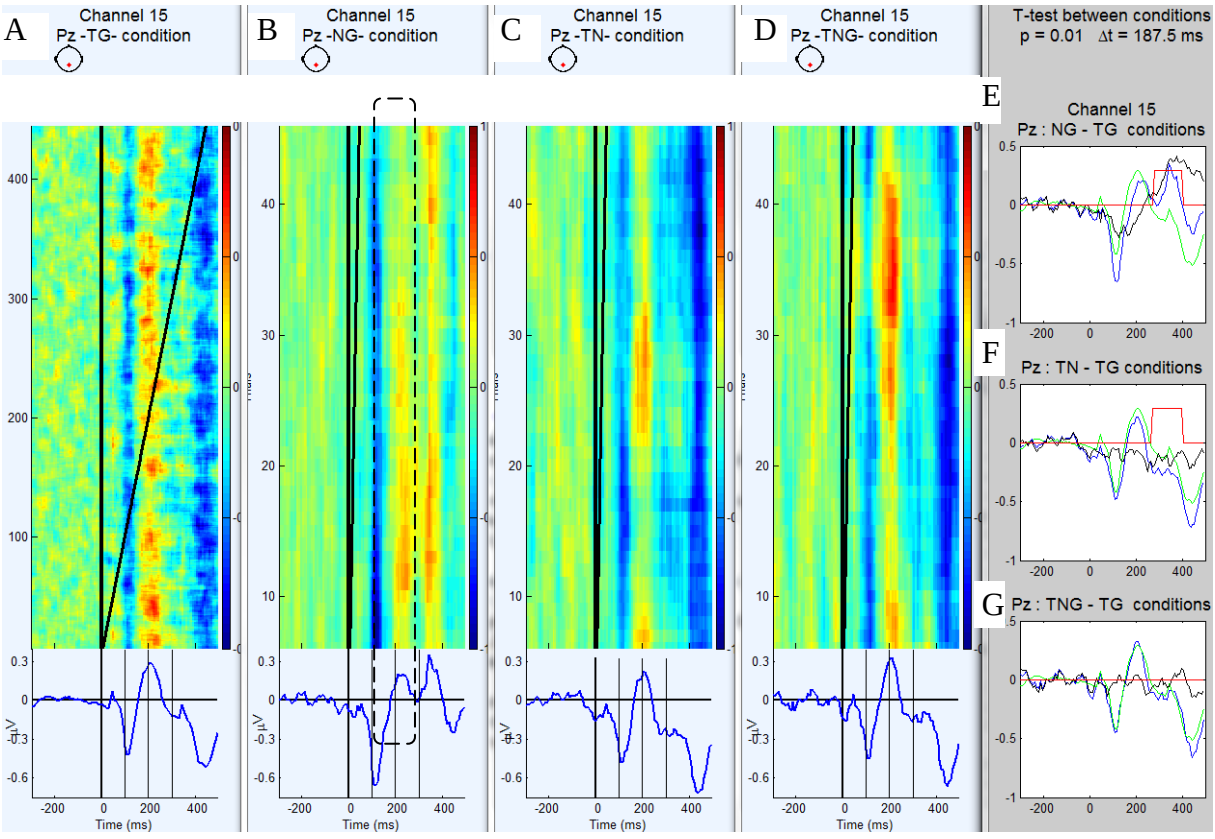


Figure 10 (A-D) Grand average ERP waveforms and trial by trial voltage plots at Pz electrode in 12 participants diagnosed with schizophrenia in the standard goal (TG), novel preceding goal (NG), novel target (TN) and simultaneous novel and goal (TNG) conditions. (E-G) Waveforms generated by subtraction (in black) of novel conditions from control condition (TG in green) and corresponding t-values for successive time bins of 187.5 ms

The ERP difference TN-TG condition shows that the brain response of the controls is significantly more negative than that of the schizophrenics during the early part of the response to a novel stimulus that has replaced a goal stimulus. This suggests that the schizophrenic participants may be producing a smaller MMN to the novel S2 stimuli consistent with previous research auditory deviants in visual task in schizophrenic patients (Catts et al., 1995) and auditory deviant in auditory task in schizophrenic patients but not in bipolar and depressive patients (Umbricht et al., 2003).

2.3.3 Single Trial across-subject comparisons of P300 amplitude and Intertrial intervals for novel stimuli.

Peak amplitude of the EEG in the latency window 250 ms to 450 ms in each NG trial in the experiment was determined and is illustrated in Figure 11 for controls and Figure 12 for individuals with a diagnosis of schizophrenia and independent sample t-tests were used to find whether the mean across-subject amplitude differed from NG trial to NG trial at Fz, Cz, Pz.

It was evident that there were statistically significant differences between some pairs (***Figure 12***, left part) but little evidence of habituation of P300 amplitude over the time after the initial NG trial. When we arranged the number of trials between 2 preceding novel stimuli vs. amplitude of the P300 peak in Fz, Cz, Pz (***Figure 12***, central part), no pattern of increase, decrease or oscillation of the amplitude of the P300 peak was found. A bootstrap correlation (1000 random resamples) was run on data from channels Fz, Cz, Pz, CP6 and CP5, between the amplitude of the P300 peak and the number of trials between 2 preceding novel trials (***Figure 12***, right part) and a significant correlation of 0.4 was observed at the central electrode Cz.

In summary, it was found that that amplitude of P300 peak did not decrease over the duration of the experiment. Fluctuations in P300 amplitude were shown to be correlated with interval size between successive NG trials at Cz.

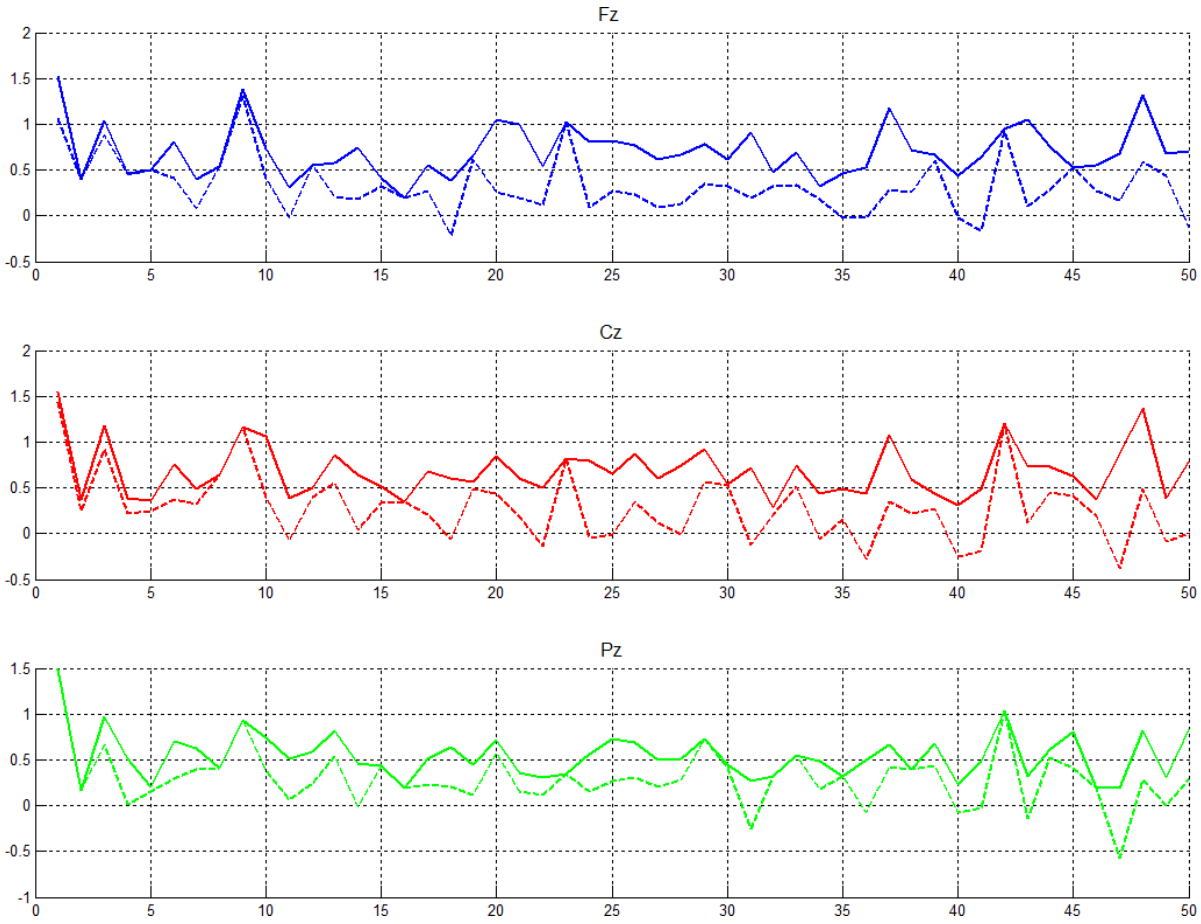


Figure 11 Preceding novel stimuli (NG) vs. amplitude of the P300 peak in Fz, Cz, Pz. P300 peak amplitudes between 250 ms and 450 ms (solid lines) and between 350 ms and 450 ms (dotted lines) computed for control participants.

Peak amplitudes in five channels between 250 ms and 450 ms and between 350 and 450 ms were computed for both groups of controls and schizophrenic patients. Those amplitudes were correlated with the time between novels, bearing in mind the previous novel trial can be any of the TN, TNG or NG conditions. Our analysis addressed two possibilities for the effect

of time between novel stimuli defined by number of trials: (1) between the previous NG and the current NG, and (2) any novel (NG, TNG or TN) that is the closest to the current NG (see Table 3).

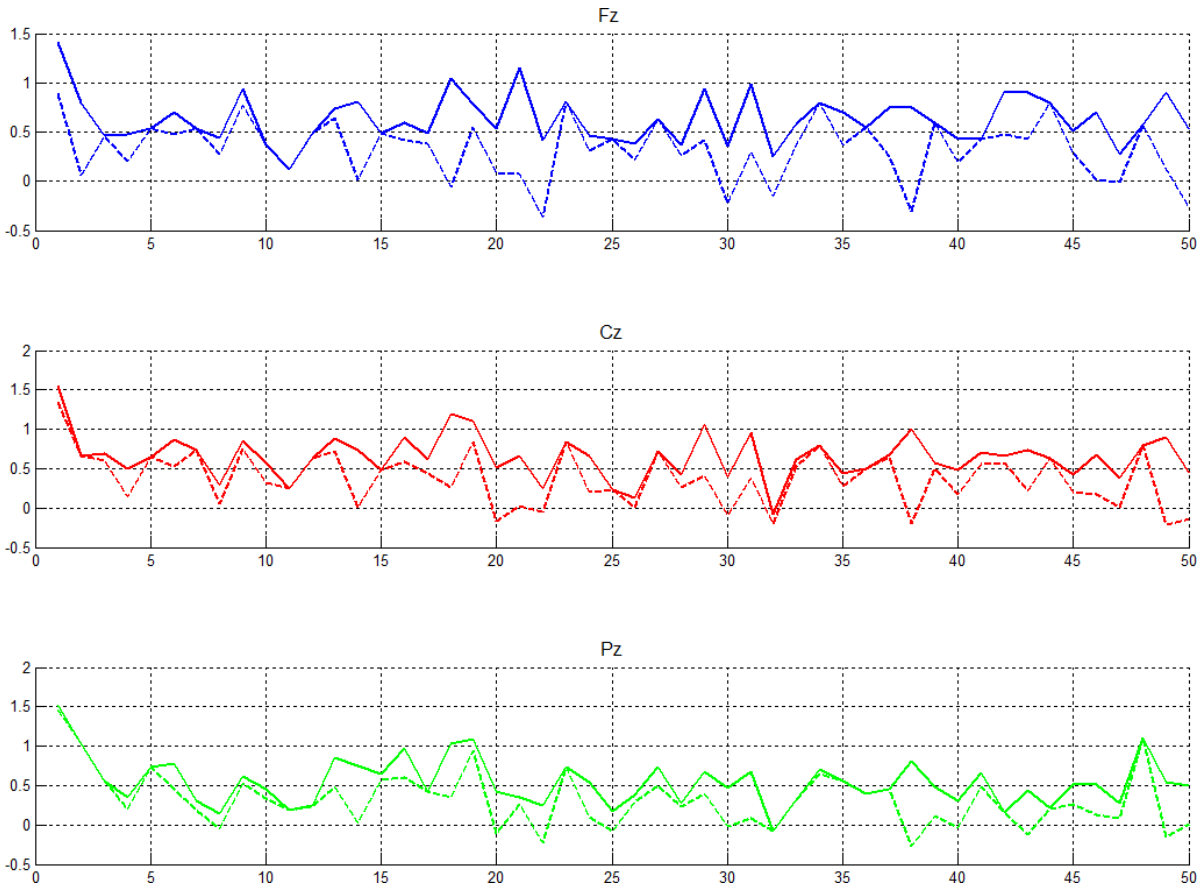


Figure 12 Preceding novel stimuli (NG) vs. amplitude of the P300 peak in Fz, Cz, Pz. P300 peak amplitudes between 250 ms and 450 ms (solid lines) and between 350 ms and 450 ms (indented lines) computed for schizophrenic patients.

We found that the P300 amplitude varied significantly with Inter-Stimulus Interval. In control participants correlations between any previous novel and the current NG condition and the peak amplitudes computed between 250 and 450 ms in controls was found significant in CP5 (r = -.27, p = .0317, highlighted in Table 3). On the other hand, schizophrenic patients showed significant correlations in Fz and Pz (r =.27, p = .01915 in Fz and r =.30, p = .0067 in Pz, highlighted in Table 3) when correlations were computed between two NG conditions for

peak amplitudes between 250 ms and 450 ms. No significant correlation difference was found in the other times, namely from 350 ms to 450 ms.

Table 3

Correlations between peak amplitude in EEG channels Fz, Cz, Pz, CP5 and CP6 and time between Novels.

Controls (n = 20)					Schizophrenic patients (n = 12)				
Peak between 250 ms and 450 ms. NG to next NG					Peak between 250 ms and 450 ms. NG to next NG				
Channel	r	p	CI1	CI2	Channel	r	p	CI1	CI2
Fz	0.211	0.150	-0.323	0.622	**Fz**	**0.279**	**0.019**	**-0.148**	**0.642**
Cz	-0.019	0.878	-0.473	0.471	Cz	0.182	0.100	-0.210	0.562
Pz	-0.083	0.589	-0.552	0.451	**Pz**	**0.307**	**0.007**	**-0.100**	**0.644**
CP5	-0.144	0.289	-0.539	0.348	CP5	0.148	0.230	-0.294	0.580
CP6	-0.040	0.801	-0.538	0.544	CP6	0.219	0.080	-0.223	0.607
Peak between 350 ms and 450 ms. NG to next NG					Peak between 350 ms and 450 ms. NG to next NG				
Channel	r	p	CI1	CI2	Channel	r	p	CI1	CI2
Fz	-0.087	0.662	-0.613	0.570	Fz	0.163	0.194	-0.278	0.589
Cz	0.053	0.763	-0.491	0.576	Cz	0.072	0.577	-0.391	0.500
Pz	0.128	0.425	-0.447	0.634	Pz	0.188	0.131	-0.259	0.615
CP5	0.048	0.731	-0.415	0.537	CP5	0.074	0.589	-0.448	0.556
CP6	-0.023	0.900	-0.507	0.524	CP6	0.254	0.049	-0.206	0.693
Peak between 250 ms and 450 ms. Any novel to next NG					Peak between 250 ms and 450 ms. Any novel to next NG				
Channel	r	p	CI1	CI2	Channel	r	p	CI1	CI2
Fz	-0.130	0.428	-0.605	0.471	Fz	-0.016	0.901	-0.520	0.455
Cz	-0.134	0.420	-0.689	0.411	Cz	-0.001	0.997	-0.510	0.479
Pz	-0.168	0.265	-0.621	0.370	Pz	0.032	0.818	-0.459	0.488
CP5	**-0.272**	**0.032**	**-0.625**	**0.208**	CP5	-0.118	0.300	-0.498	0.296
CP6	0.080	0.685	-0.503	0.602	CP6	-0.032	0.835	-0.478	0.517
Peak between 350 ms and 450 ms. Any novel to next NG					Peak between 350 ms and 450 ms. Any novel to next NG				
Channel	r	p	CI1	CI2	Channel	r	p	CI1	CI2
Fz	0.115	0.469	-0.480	0.560	Fz	0.014	0.908	-0.403	0.513
Cz	-0.064	0.674	-0.613	0.463	Cz	-0.083	0.561	-0.526	0.413
Pz	-0.013	0.913	-0.583	0.515	Pz	0.094	0.505	-0.362	0.561
CP5	-0.082	0.608	-0.617	0.490	CP5	-0.135	0.365	-0.590	0.419
CP6	0.090	0.594	-0.481	0.600	CP6	0.196	0.142	-0.278	0.620

r : Bootstrap correlation

p: Significance of the value of the bootstrap correlation

CI1: Lower confidence interval value at 95%

CI2: Lower confidence interval value at 95%

Statistical values (r, p, CI1 and CI2) were computed with 5000 resamples under bootstrap calculi

2.3.4 Single trial approach: Correlations between preceding novel P3a amplitudes and stimuli sequence and sound properties.

The aim of this analysis is to dissociate P3a amplitude fluctuations that result from stimulus properties from group differences in attention orienting. Therefore the correlations between preceding novel P3a amplitudes and stimulus sequence and the correlations between preceding novel P3a amplitudes and stimulus sequence were computed. An analysis for the effects of sound measures including their relationship to preceding sounds in the design of the experiment demonstrated that sound properties did not differ between the sounds presented to the right and left ears (detailed results of these calculations are not presented here). The 50 preceding novel stimuli were split into 2 classes to analyse possible effects of stimulus differences. There were: 26 white noise stimuli with the same duration and few changes in amplitude, and 24 'environmental sound' stimuli.

A bootstrap correlation of sound properties of one or both stimuli (preceding novel and target number) with the across participant single trial EEG average in control (n=20) and schizophrenic patient groups (n=12) was computed. Table 4 illustrates these properties which consist of 14 measures computed from the current condition between the cue (preceding novel or tone) and target (goal / goal with novel / novel). In *Figure 13* the amplitude of correlations between across-subject single trial P300 amplitude and the 14 stimulus properties (Table 4) are illustrated for each condition TG, TN, TNG and NG considering when the Novel is either the white noise or the environmental sound. The magnitude of the correlation is indicated in colour (see legend in *Figure 13*)

Table 4

Sound properties explored on the events of the experiment.

Stimuli name	Number of presentations
Freq(S1)	Frequency of S1
Dura(S1)	Duration of S1
Rms(S1)	Root mean square (RMS) in time of S1
Std(S1)	Standard deviation of S1
Freq(S2)	Frequency of S2
Freq(S1-S2)	Frequency of S1 - frequency of S2
Dura(S2)	Duration of S2
Dura(S1-S2)	Duration of S1 - duration of S2
Ltas(S1,S2)	Average difference in the long term average spectrum between S1 and S2
Entr(S1, S2,)	Normalized mutual information in frequency between S1 and S2
Rms(S2)	Root mean square (RMS) in time of S2
Std(S2)	Standard deviation of S2
Rms(S1-S2)	Root mean square in time of S1 - Root mean square in time of S2
Std(S1-S2)	Standard deviation of S1 - standard deviation of S2

In the control group, in *Figure 13* (top) the correlations are stronger at the parietal channel (Pz) in the simultaneous novel and goal conditions. This correlation is slightly stronger when either white noise or environmental sound is considered across these control participants. However, in control participants, the correlations between sound properties and P300 amplitude are not consistently spread across those 5 channels in this analysis (horizontally in *Figure 13*) and that means single electrodes activated on an specific time.

In the schizophrenic patients group, as shown in *Figure 13* (bottom), the correlations in the first 4 conditions were not spread across electrodes or in the white noise condition. Unlike the control group, in the 'environmental sounds' the schizophrenic group showed significant correlations across at least 3 electrodes analysed. In other words, for the schizophrenic group, when the warning signal is replaced by an environmental sound as a preceding novel distractor, the effect of duration of the sound is a significant negative correlation spread over all 5 channels of analysis. In contrast, the mutual information of frequency (LTAS) or entropy between S1 and S2 and the amplitude of P300 is strong and positive.

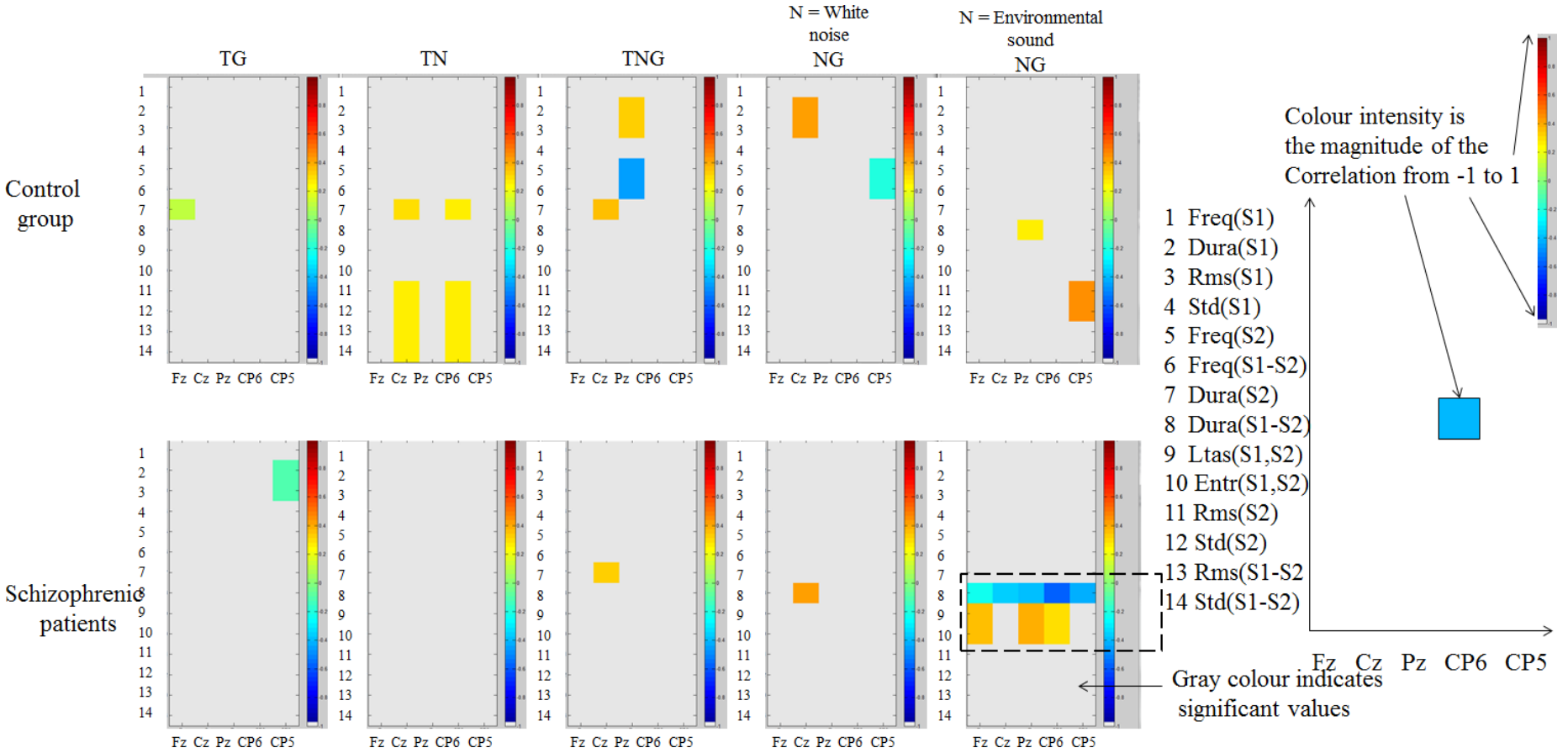


Figure 13 Correlations in control participants & schizophrenic patients (shown in colour) between amplitude of single trial across-subject P300 peak at channels Fz, Cz, Pz, CP6 and CP5 (horizontal axis) and fourteen sound properties (vertical axis). P300 amplitude measured in the time range [250 450] ms. Difference of duration and spectrum calculations (LTAS and entropy) showed correlations across electrodes in the analysis only in schizophrenic patients.

Due to the small sample size in both groups, correlations between groups are not possible to compare with Z-Fisher correlations. For example, when the Z-Fisher correlations in schizophrenic patients are between -.3 and -.6 and when the sample size (n = 12) is computed against $r = 0$ for control group (n = 20) this results in non-significant correlation differences.

A bootstrap correlation of previous properties of one/both stimuli (preceding novel and goal number) with the current EEG average in the task in control participants was also carried out, to explore why local probability and sound properties do not correlate with changes in P300 amplitude. Correlations between P300 amplitude over electrodes Fz, Cz, Pz, CP6 and CP5 and sound properties were computed for two ranges of time: [350, 450] ms and [250, 450] ms. To explore in more detail the nature of the correlations with the first 14 parameters used before, these 40 additional correlations described in Table 2 were computed separately for novel sounds presented to the left or right ear. Because of the 10 sound properties in the 4 additional comparisons, there are several groups of correlations. Bearing in mind whether white noise or environmental noise is analysed and peak amplitude or peak latency four analyses may be done:

First, the correlations were computed between the sound properties of 26 white noise preceding novel stimuli and amplitudes of P300 (detailed results of these calculations are not presented here) and showed that left ear stimulation produces many significant and strong P3a correlations and many of them are correlated between the same sound pairs. This occurs across a wide range of computed sound properties and they are stronger in: Cz, Pz, CP6 and CP5 for sounds present on the left ear, Fz, Cz, Pz, CP6 for sounds present on the right ear when the properties are related to previous novel sounds.

We can also add the point of view of the sound properties: Left Amplitude of S1 is consistently activated in three electrodes with the current goal or either warning signal or goal in the previous trial, and left LTAS is consistently activated in four electrodes when the calculation is done without the previous NG. Both properties are more consistently activated between 350 and 450 ms, *i.e.* when S2 is in its first 100 ms, and relative Duration of the current S1 to the previous S1 or the previous Novel S1 in the case of time from 250 ms to 450 ms. On the other hand, the relative frequency differences between the current Novel and the previous Novel resulted in the appearance of single trial average ERP fluctuations over the right frontal scalp sites.

When the results of correlations of stimulus properties and peak amplitudes are computed in the ranges between 250 and 450 ms and between 350 and 450 ms, it seems to be a fronto-central negativity that affects correlation with the previous cue, but not with the previous target for both left (relative sound amplitude) and right (relative sound duration) ear.

Second, Figure 14 A and B shows the results of correlations between the sound properties of 24 environmental sound stimuli as preceding novel stimuli and the amplitude of P300 over 5 electrodes, measured respectively as the local maximum between 250 and 450 ms range, and 350 and 450 ms range.

It is apparent in the case of responses to environmental sounds that between 250 and 450 ms after stimulus onset there are more correlations at CP5 than when the time was between 350 and 450 ms and in both cases there are only correlations at CP6 (and not at CP5) when the stimuli are correlated only on the right side. This suggests that, in contrast to white noise, these stimuli evoke right lateralised responses that are modulated by several sound properties.

It is also apparent that Amp(S2) modulates responses at CP6 and combined measures between S1 and S2 appears only when time is between 250 and 450 ms, but other sound measures appear correlated between 350 and 450 ms. Considering the environmental sound as a non-frequent Novel Sound, although scalp EEG does not inform about brain source these results would be consistent with the idea that the right temporo-parietal junction is related with attention to the Novel stimulus (Corbetta, Patel & Shumann, 2008). Stimulus duration for S1 is highly correlated with P300 at right temporal and parietal electrodes. Figure 14 C and D show that for duration, white noise stimuli compared with the preceding novel presented to the left ear is correlated with single trial average P300 amplitude at electrode CP6, and at Pz electrode when the sound is presented to the right ear at electrode Pz. Bearing in mind the number of channels for choosing possible predictors for peak amplitudes, this analysis did not show LTAS affecting P300 with Novel events in previous trials.

A third set of correlations between the sound properties of 26 white noise stimuli as preceding novel stimuli and latency of P300 peak over 5 electrodes, measured respectively as the local maximum between 250 and 450 ms and also for the time window from 350 to 450 ms. Correlation results appeared different from the range of [250, 450] ms when the time window of the P300 peak is correlated with lateralized sound properties in the time range of [350, 450 ms]. Although in the case of sounds presented to the left or the right ear, correlations are not present in more than 2 channels, and the difference in the overall signature is different. The other results related to the latency of the P300, either positively with Duration and negatively with Root Mean Square of the Goal, are for both left and right sounds from 250 to 450 ms and not significant from 350 to 450 ms. This means that possibly these measures are influenced by the presence of a larger N100 evoked by the Goal.

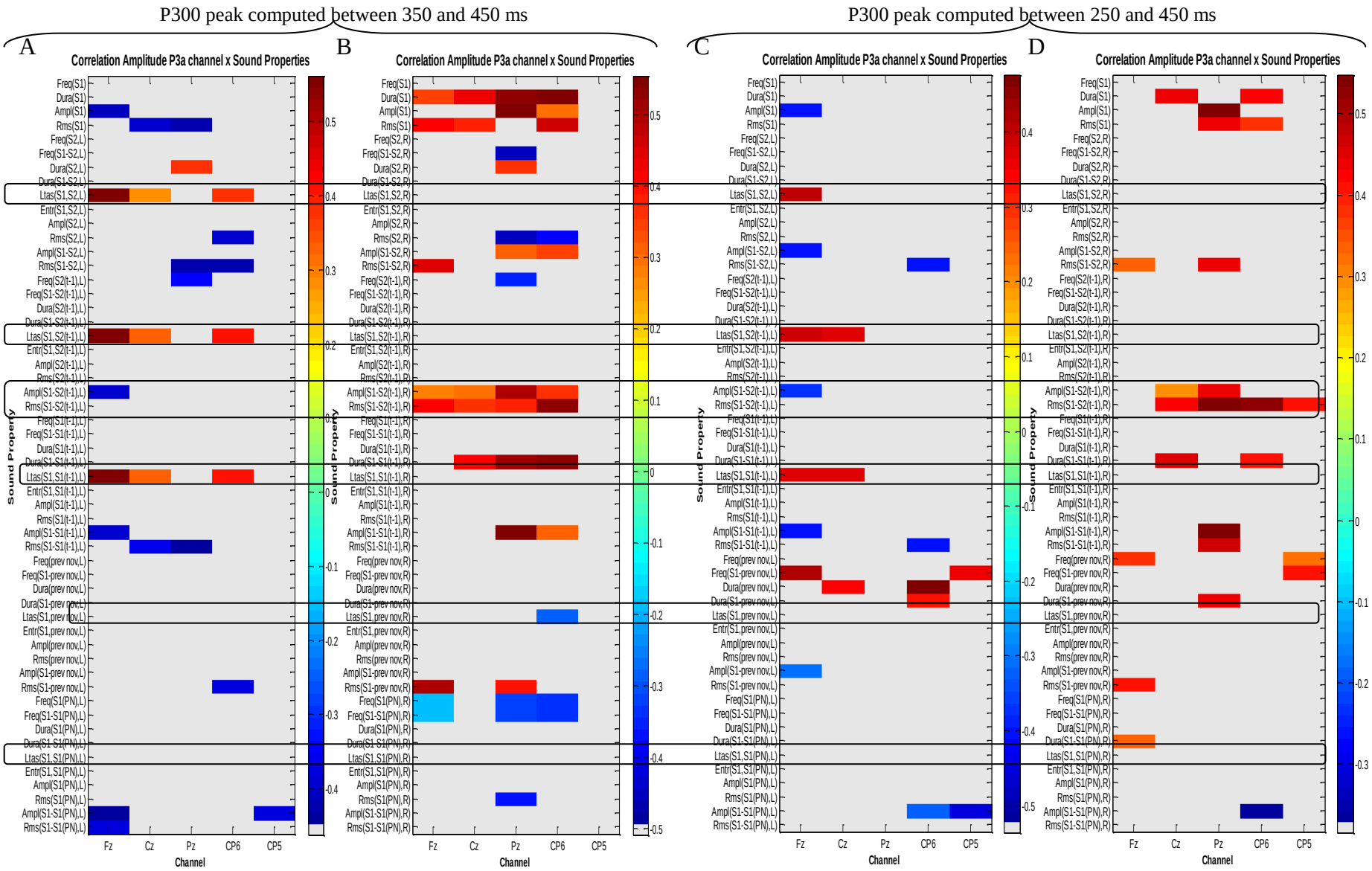


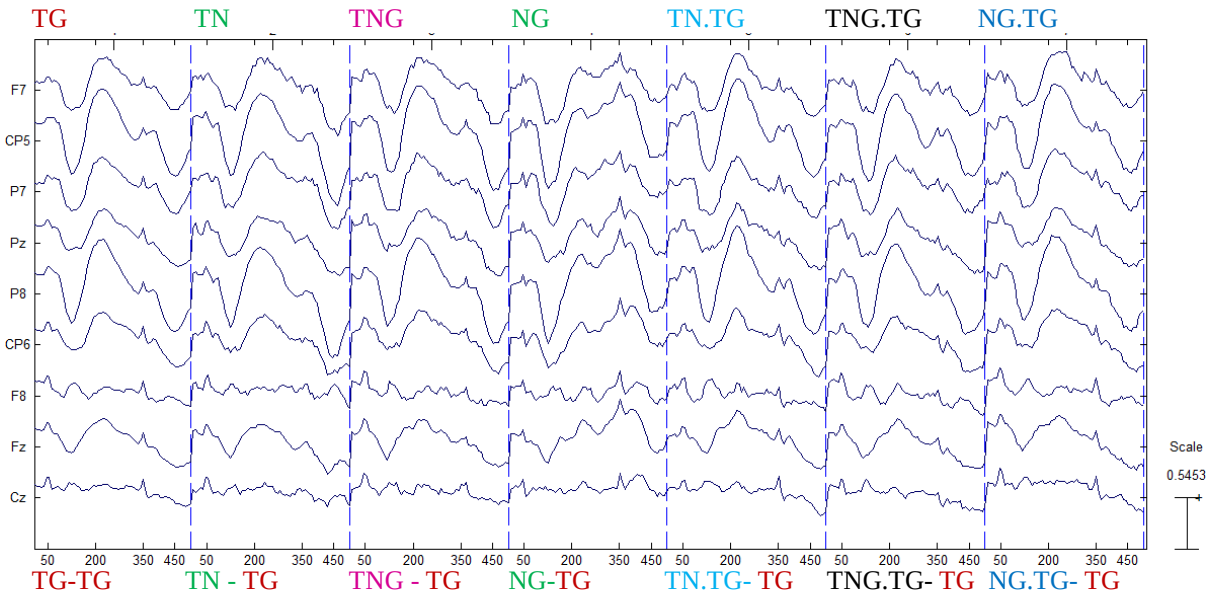
Figure 15 Correlations of the amplitude of the P300 peak and several sounds properties when the environmental sound is presented on the left (A and C) and right (B and D). Note that correlations for sounds on the right ear are right lateralized without correlations in CP5 and on the left ear there is mostly correlations with the right channel and only one with the left channel. *C,D* Note that here results are not lateralized, but with regard to the right ear, correlations are mainly negative with one positive correlation at right electrode CP6.

A fourth set of results of the correlations between the sound properties of 24 environmental sounds as preceding novel stimuli and the latency of P300 at 5 electrodes. Although in the case of sounds presented to the left or the right ear, correlations are not present in more than 2 channels except for LTAS (S1,previous novel), having correlations less than 0.2. Only single trial average ERP latencies at electrode CP6 were significantly correlated with the duration of preceding novel white noise when compared to the previous novel showing a right lateralised effect. Single trial average ERP latencies at CP5 were correlated with both left and right lateralised distractor sounds in the time window 350 to 450 ms, while there is no similar signature between 250 and 450 ms. It can be seen in the time range between 250-450 ms that the correlations for sound on the right ear are right lateralized with a similar signature to correlations in CP5.

2.3.5 Conditions and stimulus sequence contextual on ERPs in controls and schizophrenic patients' groups.

The previous analyses indicated that there are correlations between several sound properties of the prior stimulus and the P300 amplitude. This was explored further by producing new averages of the control condition responses separated on the basis of which experimental condition that control trials followed. This procedure rendered seven conditions: Tone-Goal preceded by Tone-Goal (TG.TG), Tone-Goal preceded by Tone-Novel (TN.TG), Tone-Goal preceded by Tone-simultaneous Novel / Goal (TNG.TG), Tone-Goal preceded by Novel-Goal (TG.NG), Tone-Novel preceded by Tone-Goal (TG.TN or TN), Tone-simultaneous Novel / Goal preceded by Tone-Goal (TG.TNG), Novel-Goal preceded by Tone-Goal (TG.NG).

The control group showed significant differences, mainly in the range of time normally associated with perceptual and stimulus-driven processes. *Figure **15*** shows that the difference with the standard stimulus was not only for the other three different conditions (TN, TNG and NG) but also when the condition of the preceding couple of sounds was taken into account (namely TN, TNG, and NG). The standard ERP was subtracted from the other ERP conditions to emphasise the differences between conditions (*Figure **15**, middle*). Finally, multiple one-tailed t-tests between each condition and the standard condition were calculated ($p<.001$, uncorrected) to determine the significant differences in time and across channels (*Figure **15**, bottom*). Significant differences are shown in TN-TG, TNG-TG and NG-TG as expected. These differences were stronger in the [200, 350] ms range of ERP difference NG.TG was shown significant different from TG.TG mostly at right lateralized electrodes, see Figure **15**, bottom in dashed lines. Bearing in mind the ERP answer on the electrodes on the top, it may suggest a kind of positivity response for S1 and the P50 for S2



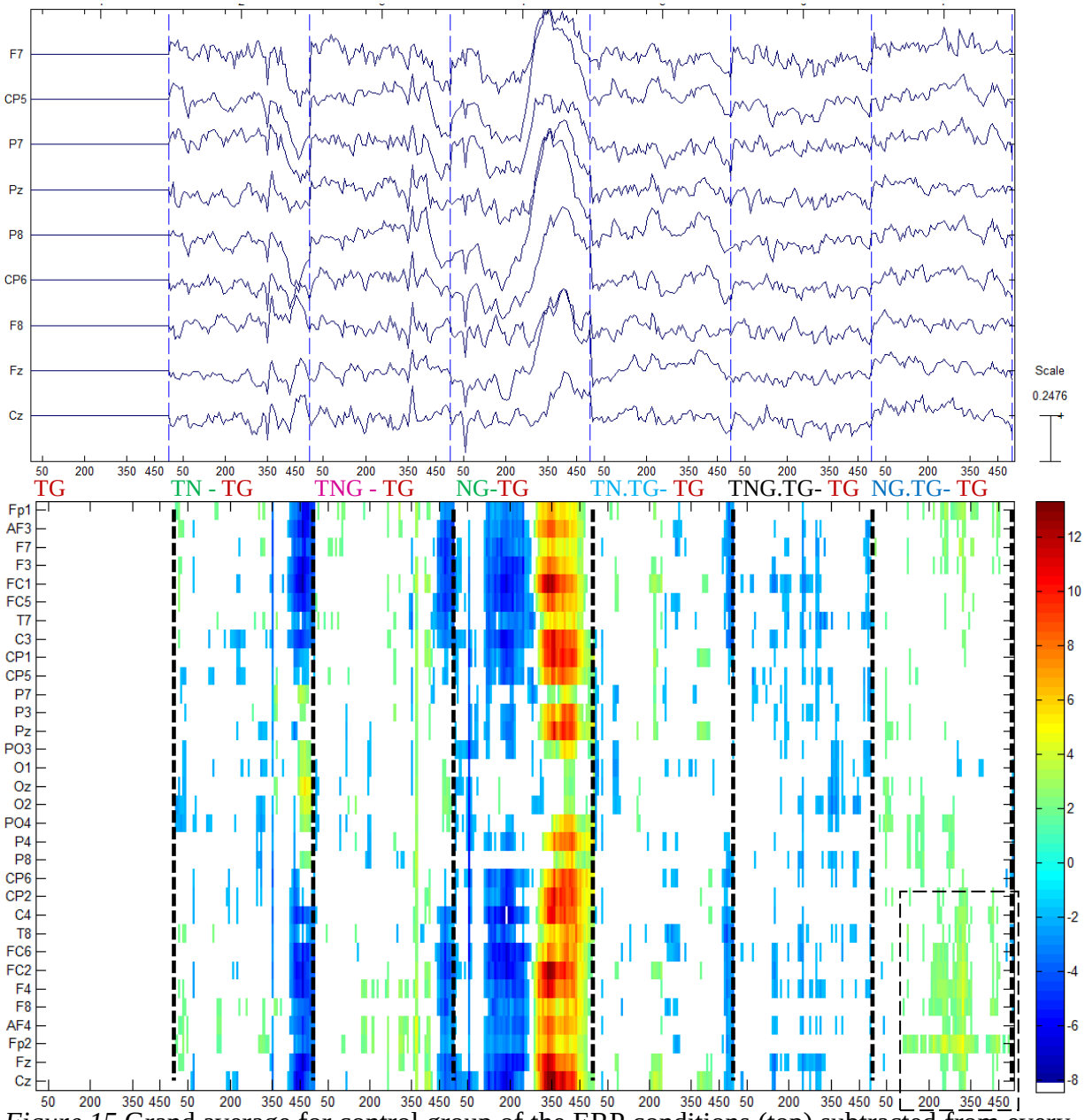


Figure 15 Grand average for control group of the ERP conditions (top) subtracted from every ERP condition in the previous channels (middle), and the one-tailed t-test analysis between each condition and the standard followed by the standard (p<.001) (bottom)

In the case of schizophrenic patients, significant differences occurred at the time that can be attributed to gating of sounds (P50) either in the first or second stimulus, this is shown in the NG – TG plot in ***Figure 16***. Similar to the control participants, ***Figure 16*** shows that the difference with the standard stimulus was not only for both different conditions but also in

the standard condition split into those four conditions relying on the condition of the preceding couple of sounds.

The schizophrenic patients showed significant differences, mainly in the range of time normally associated with perceptual and stimulus-driven processes. Figure 16 shows that the difference with the standard stimulus was not only for the other three different conditions (TN, TNG and NG) but also when the condition of the preceding couple of sounds was taken into account (namely TN, TNG, and NG). The standard ERP was subtracted from the other ERP conditions to emphasise the differences between conditions (Figure 16, *middle*). Finally, multiple one-tailed t-tests between each condition and the standard condition were calculated ($p<.001$, uncorrected) to determine the significant differences in time and across channels (Figure 16, *bottom*). Significant differences are shown in TN-TG, TNG-TG and NG-TG as expected by the impairment hypothesis (H3). Bearing in mind time range of more than 50 ms of difference, the NG.TG was not shown significant different from TG, instead TN.TG and TNG.TG were different.

Overall, it was found that the sequence effects in contextual sorted ERPs indicate a difference in these groups. Whether in control and schizophrenic patients, the previous stimulus significantly affects the following standard condition ERP deflections.

Although we can use false positive correction this was not run for the between-group analysis in this single trial approach, due to the small number of schizophrenic patients (n=12) and the lack of multicomparison techniques, similar to the correlation analysis.

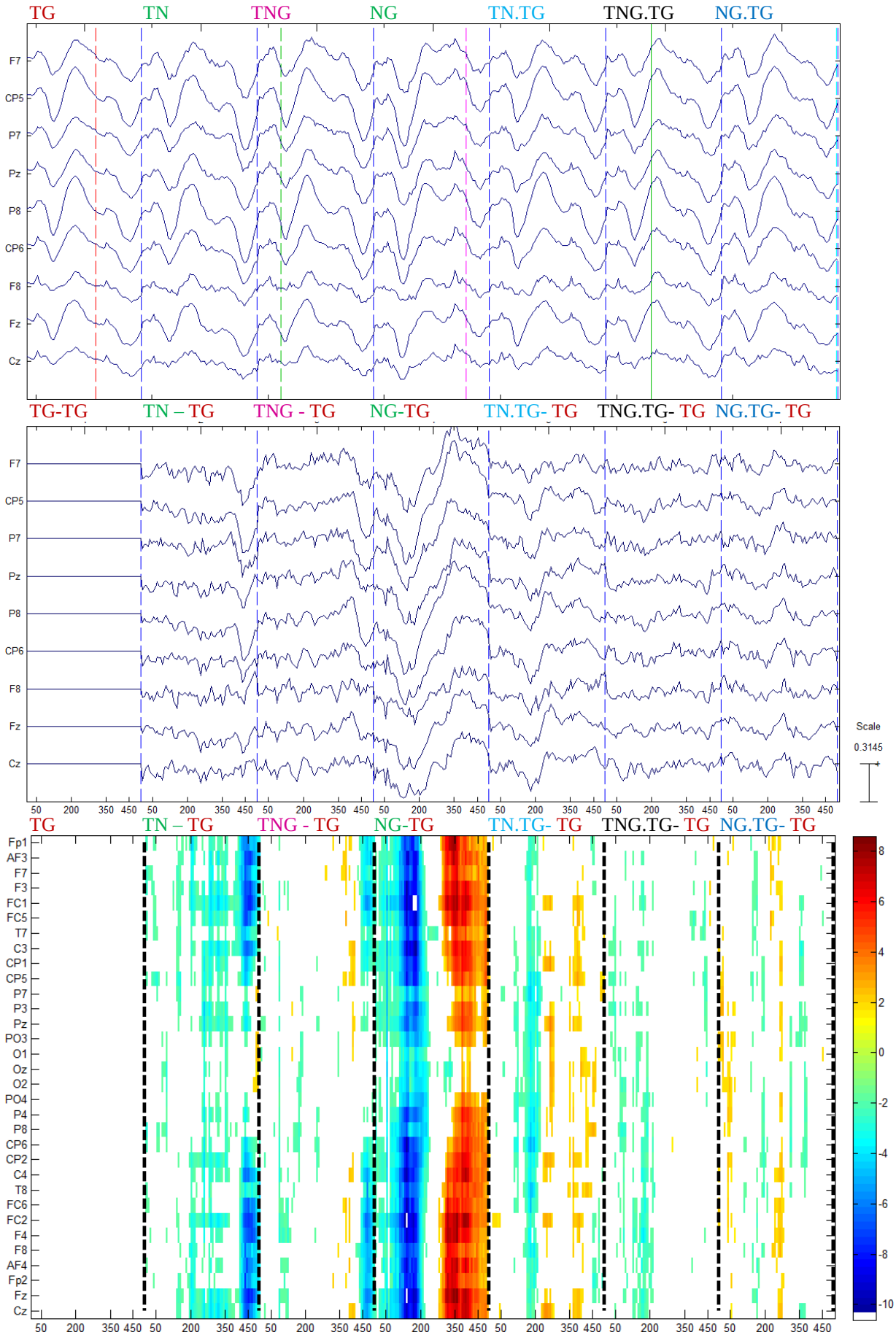

TG
TN
TNG
NG
TN.TG
TNG.TG
NG.TG
F7
CP5
P7
Pz
P8
CP6
F8
Fz
Cz
TG-TG
TN – TG
TNG - TG
NG-TG
TN.TG- TG
TNG.TG- TG
NG.TG- TG
Scale
0.3145
Fp1
AF3
F7
F3
FC1
FC5
T7
C3
CP1
CP5
P7
P3
Pz
PO3
O1
Oz
O2
PO4
P4
P8
CP6
CP2
C4
T8
FC6
FC2
F4
F8
AF4
Fp2
Fz
Cz
50 200 350 450

Figure 16 Grand average for schizophrenic patients of the ERP in each condition (top) subtracted with the standard ERP condition in the previous channels (middle), and the multiple t-test analysis between each condition and the standard followed by the standard (p<.001) (bottom).

2.3.6 Stimulus sequence and sound properties on the ERP.

In an attempt to improve the explanation of the single trial averaging results from P300 amplitudes to the whole ERP waveform a new analysis was carried out using LInear MOdelling (LIMO) for EEG data (Pernet et al., 2011). This is based on the strongest significant values for Percentage of the variance (R2). For each subject, a design matrix was created that included the experimental conditions as categorical variables. LIMO was run for all conditions and R2 values were less than 0.15 for every participant.

First, both groups and the four conditions in a 2 x 4 ANOVA were explored. The F values for each electrode in each time bin are illustrated in *Figure 17*. Comparisons of the Difference between conditions revealed a significant difference in the ranges of 0 to 50 ms and from 100 ms to 150 ms (stimulus detection), and also in the time window 184.38 ms to 215.63 ms (range between perception and mismatch negativity).

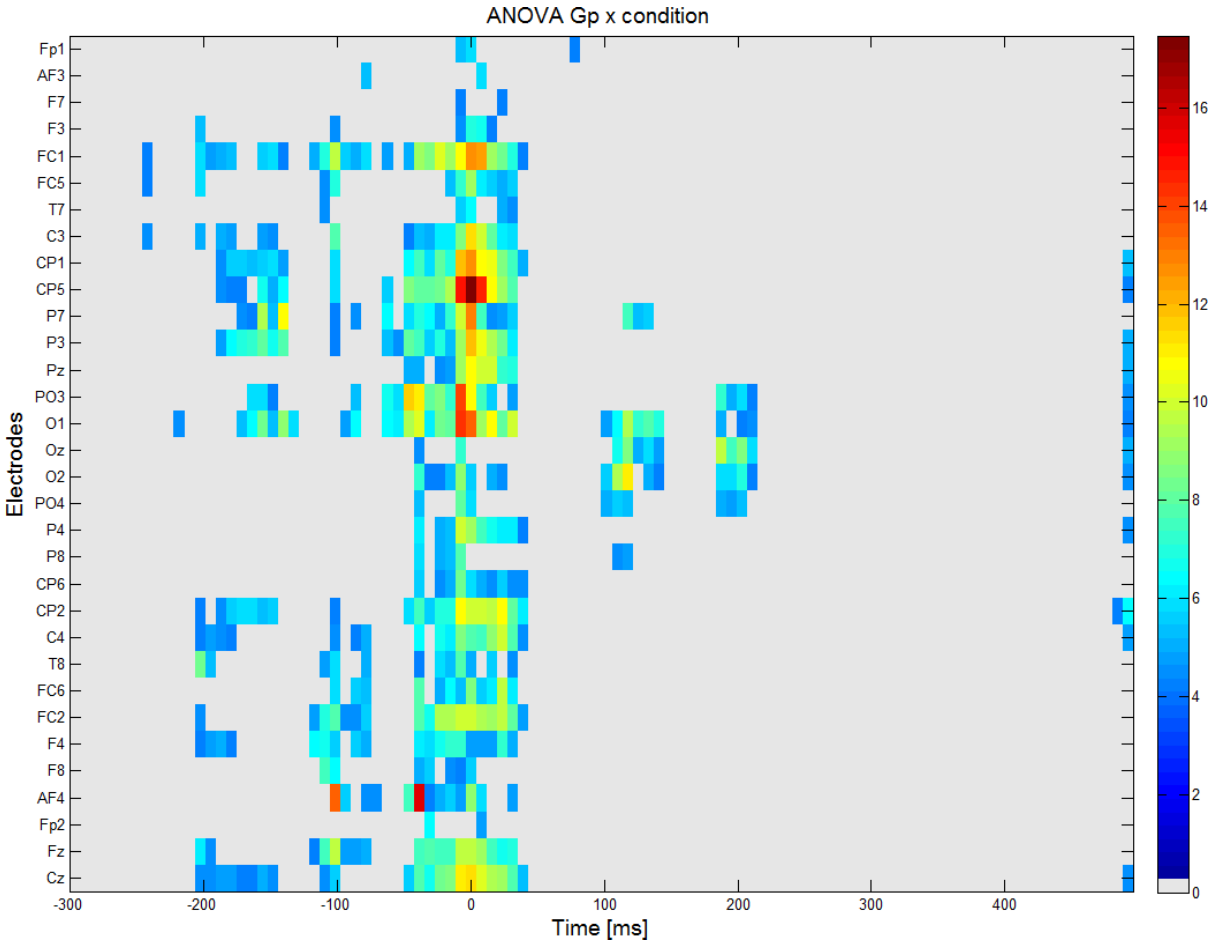


Figure 17 Second level analysis in the 2 groups x 4 conditions ANOVA Values in colour for the F value explained for the TG, NG, TNG and NG conditions.

Bearing in mind the previous results, the multiple one-sample t-test was run in each group to explore in each condition two issues: first, to determine the significance of the ERP wave differences, and also by using the regressor in the analysis. Second, a multiple Two-sample T test was run in order to find the differences between Control participants and Schizophrenic patients.

In the TG condition for control participants and schizophrenic patients, the T-values based on time per electrodes using LIMO were done in each group. Results of multiple one-tailed T test reported similar deflections for both groups positive deflections in the ranges from 50 to

100 ms (stimulus detection) and from 170 ms to 270 ms and negative waves in the time window from 90 ms to 140 ms (range between perception and mismatch negativity) and from 300 ms (controls) and from 320 ms (schizophrenic patients). This confirms that the tone does not produce a significant P300 response, but the tone produces a strong response around 220 ms (controls) and from 200 ms (schizophrenic patients). When the difference between both groups was calculated, this revealed right lateralized differences between 86 and 156 ms (detailed results of these calculations are not presented here). Therefore, these results suggest a difference in the N100 response. There is also a small window time of difference at 351 ms. The greatest T-values were around 3.

In the TN condition for control participants and schizophrenic patients, computation of the T-values based on time per electrodes using LIMO were done in each group. Results of ERP significance show a small positive deflection lateralized from 180 to 260 ms and negative deflections in the time from 300 ms. Negative values are from 380 ms and negative deflections are stronger from 420 ms to 460 ms (controls) and from 400 ms to 470 ms (schizophrenic patients). Again, this confirms that the Tone does not produce a significant P300 response, and the possibility that the MMN of the Novel in S2 delays the negative deflection when the result is compared with TG condition. When the difference between both groups was run using bootstrap analysis (detailed results of these calculations are not presented here), this revealed right lateralized differences between 0 and 39 ms. Therefore, the results suggest a different auditory gating response in the first 39 ms, although the greatest T-values were around 3.

In the TNG condition for control participants and schizophrenic patients, the T-values based on time per electrodes using LIMO were done in each group.. Results of multiple one T test

show right lateralized positive deflections from 180 to 260 ms (controls) and from 190 ms to 220 ms (schizophrenic patients) and negative waves from 300 ms being stronger from 430 ms to 470 ms (controls) and from 400 ms to 470 ms (schizophrenic patients). This negative deflection is possibly the MMN of the simultaneous Novel and Goal in S2. Again, this confirms that the Tone does not produce a significant P300 response, but it produces a maximum positive response at 226.6 ms for controls (absolute t-values greater than 4). When the difference between both groups was run (detailed results of these calculations are not presented here, absolute t-values close to 4) differences at 190 ms and at 398 ms appeared, although at 398 ms the difference were spread over the scalp, the results revealed a right lateralized differences between 300 ms and 440 ms. This suggest a different processing of the second stimulus for schizophrenic patients when the Novel and Goal were presented simultaneously.

In the NG condition for control participants, results of multiple one-tailed T tests show right negative values from 100 to 200 ms (absolute t-values greater than 6) and positive values from 280 ms and being stronger from 340 ms to 390 ms in controls and from 340 ms to 480 ms in schizophrenic participants (absolute t-values greater than 6). Different to the previous 3 conditions, this result confirms that the Novel produces a significant P300 response, and this is in spite of the Goal coming at 300 ms. In the comparison of the NG condition, *Figure 18* shows the T-values based on time per electrodes. Results of multiple Two-sample T-test positive waves in the time window from 20 ms to 40 ms and right lateralized 70 ms to 140 ms (range between perception) and a small bilateral positive deflection in the parietal electrodes from 398 to 430 ms. This confirms that between groups P300 is slightly different around 410 ms. Also, P50, and MMN is different for both groups. This finding would be consistent with difference in perceptual stage.

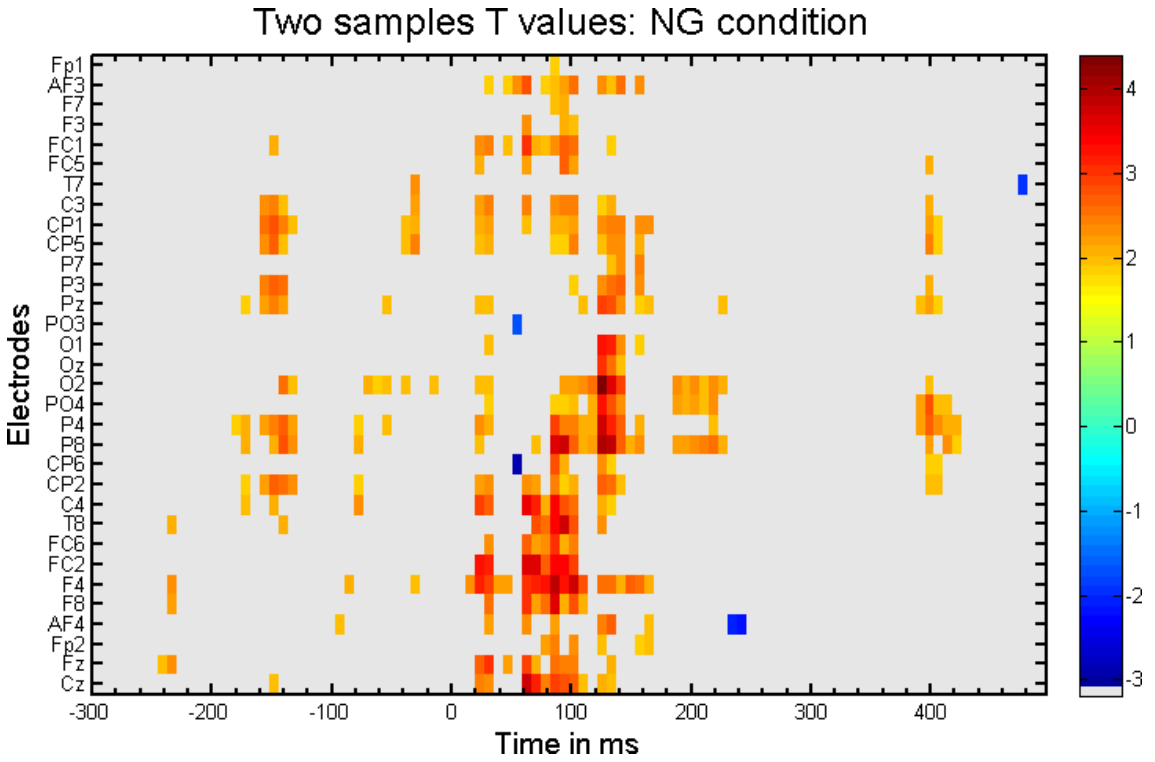


Figure 18 Comparison of the Second level analysis for NG condition comparison between Control and Schizophrenic patients. Results are based on 10,000 bootstrap mean differences. Values in colour for the T value explained for the 4 conditions plus one regressor run in the first level analysis. Note that right Positive values are across several time ranges and negative values are shown from 400 to 460 ms.

In the LTAS(S1, S2) regressor for control participants, long term average spectrum between S1 and S2, we seek for ERP significance in all trials. Therefore, *Figure 19* shows the T-values based on time per electrodes. Results of multiple one T test show right negative values from 100 to 200 ms (absolute t-values greater than 6) and positive values from 180 ms to 240 ms (absolute t-values greater than 6) and continuing up to 300 ms. This confirms that the Novel produces significant positive changes in N200 or MMN and P300 responses, and this is in spite of the Goal coming at 300 ms and also the magnitude of the T-values are similar to the magnitude of the TG condition.

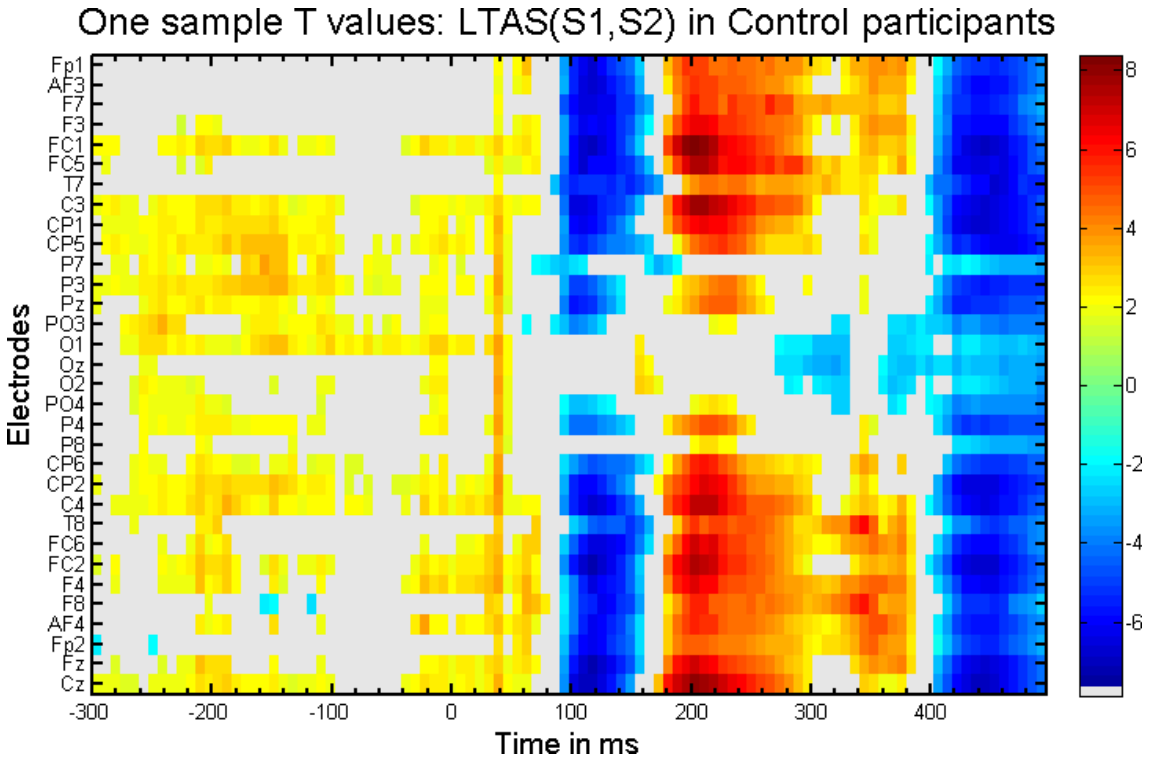


Figure 19 Second level analysis for LTAS between the warning signal sound and the Target in Control participants, bootstrapped 1000 times. Values in colour for the T value explained for the 4 conditions plus one regressor run in the first level analysis. Note time range shown of negative values from 90 to 170 ms, positive values from 190 ms to 380 ms and being stronger at around 180-240 ms.

The previous analysis was extended using the stimulus properties as the continuous regressors in the first level analysis. This is based on the strongest significant values for Percentage of the variance (R2). For each subject, a design matrix was created that included the experimental conditions as categorical regressors and the sound properties as the continuous regressors. In an attempt to distinguish group sources of variance from variance introduced by stimulus variables, every single condition was run added as covariates: firstly, each one of the sound properties (see ***Figure 20***), and secondly, pairs of sound properties in all the possible combinations worked in previous sections (Table 2). The addition of every sound property as the continuous regressor improves R2 values in several cases. Results

relating to stimulus properties are sparse. Another finding from these plots is when one looks at those stimulus properties which are not predicting the variance of the data. For example, the stimulus properties 25, 27, 31, 32, 46, 55 and 56 are not making more R2 explanation than the conditions. More interestingly, the stimulus property 50 (Entr(S1R,S1(PN)R) (see dashed line) has a good explanation of the variance in several Control participants (R2 > .3) but not in more the half of the Schizophrenic patients (R2 < .2).

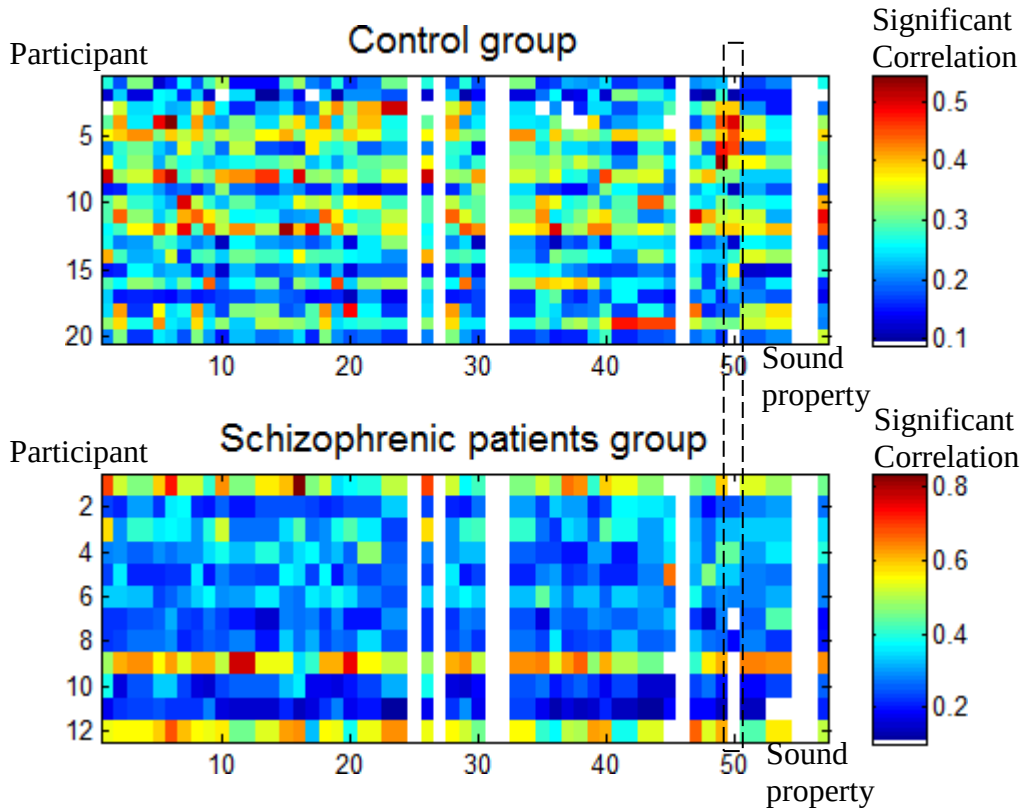


Figure 20 Maximum Percentage of the variance (R2) explained for the preceding novel condition with stimulus properties for Controls and Schizophrenic patients for NG condition. Values in colour for the peak of the Percentage of the variance (R2) are explained in text. There are few schizophrenic patients (1, 9 and 12) with greater correlation values than the control participants. The R2 was computed between 150 and 450 ms ($p<.05$). Plots show results calculated in every participant (vertical axis) for each one of the 54 regressors (horizontal axis).

The results for the selected NG condition were computed and extended to find the strongest R2 values with connectivity of 8 bins in images based on electrode and time ($p<.05$). These

calculations were done for every control participant in each of the experimental conditions (TG, TN, TNG and NG) and there were plotted of the selected R2. Different regressors were found for every one of the different conditions. Although results for all conditions together results in stimulus properties 17 to 19, 40 and 50, results about stimulus properties are sparse for the different conditions (detailed results of these calculations are not presented here). Another finding was that those stimulus properties in several cases predicted more than 30% of the variance, but not consistently across all participants. For example, the stimulus properties 1 to 4 are not showing clear R2 amounts across participants in NG and in all conditions, while they are doing in TG and TN and TNG. Also, the stimulus properties 25, 27, 31, 32, 46, 55 and 56 are not showing more R2 explanation than the conditions.

On the other hand, maximum R2 values were explored taking the greatest R2 values for 2 continuous regressors in control participants. Although the results point to subject variability across several regressors, the results also point to several better explanations of variance: for example the pair of sound properties LTAS (S1, S1 (PN)) and 'RMS (S1-S1 (PN))' as the continuous regressors. Due to the variance between conditions this analysis was not run in schizophrenic patients.

On the basis of the previous analysis, in control participants the EEG data was modelled over several parameters and the results reported one of the highest R2 for 'LTAS(S1,S1(PN)) and 'RMS(S1-S1(PN))'. These parameters fit the general lineal model approach for the preceding novel condition better, but R2 changes in different ways to electrodes and time reported for each participant (see Figure 21). Again, due to the variance between conditions this analysis was not run in schizophrenic patients.

In Figure 21, the R2 explanation of variance shows that most of the participants followed a regular pattern across several electrodes around 200 ms and between 300 ms and 400 ms. R2 for participants P51 and P56 do not have this regular pattern. This different pattern is concurrent with the behavioural facilitation observed in running average reaction times (shown previously in *Figure 8*). Therefore, these EEG analyses suggest that the change of R2 pattern comes from a different processing of the parity decision task.

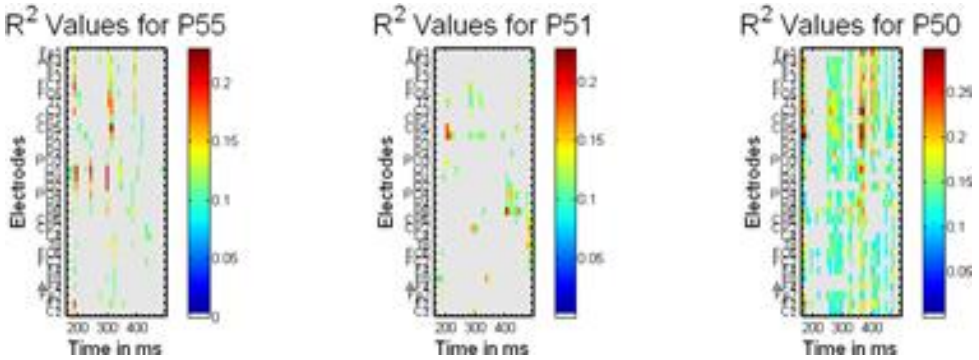


Figure 21 Amplitude of R2 points in time per each channel at every participant explained for the preceding novel (NG) condition for six of the 20 different participants, amplitude values are in colour for the R2. The R2 was computed between 150 and 450 ms taking as regressors LTAS(S1,S1(PN)) and RMS(S1-S1(PN)) (p<.05 uncorrected). For every participant the horizontal axis reports the time and the vertical axis indicates electrodes.

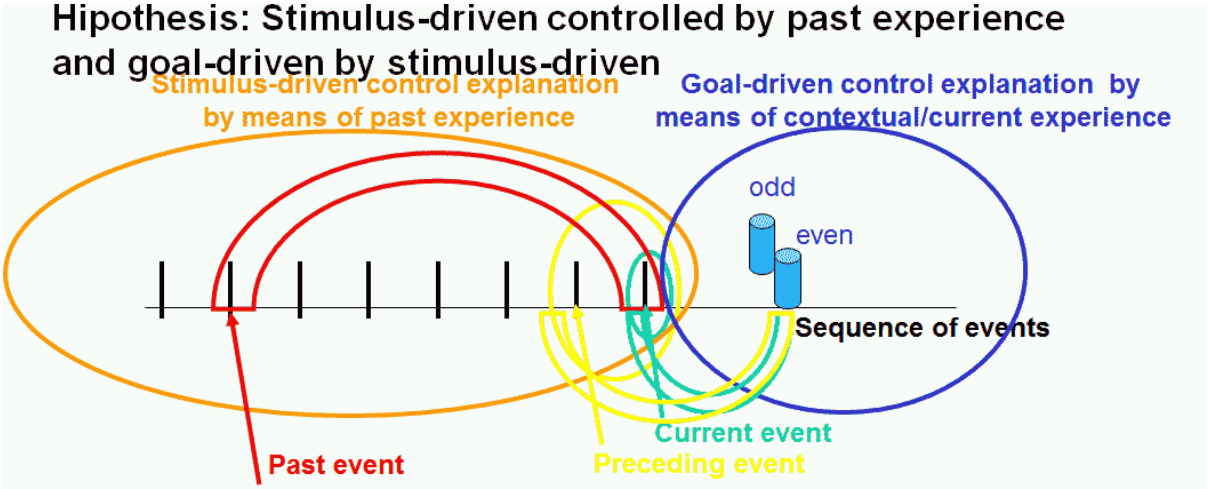
In summary, the LIMO analysis showed a great amount of results only with the conditions as the Categorical Regressors and the stimulus properties as the Continuous Regressors. First of all, we need to bear in mind the redundancy of the stimulus measures within the same sound having several high correlations of those measures (detailed results of these calculations are not presented here), but not between the sound measures of sounds of previous trials. Therefore, results pointed to different regressors in EEG Linear Modelling based on stimulus properties of the current trial, previous trials and previous novel trials. Because of the large number of results in each stimulus property in electrodes x time domain in each participant,

prior to running the second level analysis, we have tried to base the analysis on the cumulative number of significant bins that appeared for each participant's results and on the strongest explanation of variance in each participant. ***Figure 22*** the number of bins with the maximum R2 as a result of the first level analysis using LIMO are indicated. This was done in each condition and adding each one of the current 14 stimulus properties as the continuous regressors. Only the highest correlations between P300 measures and sound properties are shown in the 4 different conditions for the stimulus control of attention. For the different conditions, it is shown how the stimulus properties influence the ERP activity measured in the participants, with the greatest R2 in each participant indicated in the range between brackets. The number of bins considers the time step of analysis (7.8 ms) and the number of electrodes with a maximum in the given scale. Results pointed to stronger influence in the TNG and NG conditions in schizophrenic patients than in control participants, suggesting a higher control of the stimulus properties in schizophrenic patients than in control participants.

2.4 Discussion.

Currently, it is believed that P300 deflections consist of a P3a related to attention activation and P3b related to context-updating operations and memory storage (Polich, 2007). Potter and colleagues found ERP evidence of differences in the distribution of the P3a component (Potter et al., 2008), which suggests a dissociation of activity in the stimulus-driven (SDN) and goal-driven networks (GDN) of the attention reorienting system (Corbetta et al., 2008). In this reanalysis of data from a group of individuals with schizophrenia and a group of healthy controls the results suggest that ERP deflections are significantly influenced not just by the probability of the stimulus type (not supporting H1) but also by trial by trial differences in the frequency, duration and amplitude of the sounds (supporting H2). This analysis determine different regressors in each group in response to these other factors would

improve the specificity and/or sensitivity of the ERP analyses not only in P300 but also for MMN in schizophrenics patients (supporting H3). In summary, the original hypothesis H3 is confirmed with the reduction of MMN in controls and the tendency of the greater reduction of MMN the larger in time of the Novel for schizophrenic patients. The larger the mutual frequency information is between S1 and S2 the larger the P300 in the case of Schizophrenic patients, but not in the case of the controls Therefore the SDN attenuation highlighted by Potter et al. (2008) may be consequence of stimulus properties for the multiple condition task.



		TASK WITH FOUR CONDITIONS
Schizophrenics	R2 <0.02, 0.06> >3 bins	G: standard tone + number
Controls	R2 <0.03, 0.11> >21 bins	
Schizophrenics	R2 <0.20, 0.31> >14 bins	N: standard tone + noise
Controls	R2 <0.14, 0.40> >13 bins	
Schizophrenics	R2 <0.25, 0.82> >24 bins	S: standard tone + noisy number
Controls	R2 <0.19, 0.74> >7 bins	
Schizophrenics	R2 <0.24, 0.79> >11 bins	P: standard noise + number
Controls	R2 <0.23, 0.50> >13 bins	

Figure 22 Percentage of the variance (R2) explained for the every condition (TG, TN, TNG, NG) values for control and schizophrenic patients' groups. Also shown for R2 the significant

number of bins and range of values of R2 are indicated. The R2 was computed between 150 and 450 ms taking best regressor or couple of regressors (p<.05).

2.4.1 Behavioural results

When mean reaction times were subjected to statistical analysis, there was more slowing of reaction time in the preceding novel condition (NG) than in the simultaneous novel and goal (TNG) condition, suggesting that attention orienting occurred in the NG condition and involved a temporary shift in the mental representation of the auditory scene. Although the reaction times of the schizophrenic group were significantly slower, there was no interaction between Group and Condition. The basis of these differences was explored further by carrying out a running average analysis of individual participants and it was observed that only 15 out of 20 control participants demonstrated a consistent distraction effect.

2.4.2 ERP Results: Novelty distractor informational content and stimulus probability (H1)

The results showed that Novel P3a amplitude showed significant variation over time but did not decrease in the long-term and was not simply predicted by inter-trial intervals as predicted by Gonsalvez and Polich (2002) with small and non-significant correlations in the control participants but with significant correlations in the schizophrenic patients (around r = .3 in Fz and Pz).

The findings of P300 with significant variation with Inter-Stimulus Interval defined differently in both control and schizophrenic patients groups can reflect a different processing in this particular task. On the one hand, controls showed significant correlation to the left side (r = -.27, p = .03 in CP5); this would be consistent with attention to a known task (Corbetta & Shulman, 2002). On the other hand, schizophrenic patients showed significant correlations in

frontal and parietal electrodes (r =.27, p = .02 in Fz and r =.30, p = .0067 in Pz) which may be correlated with orienting of attention (Gonsalvez & Polich, 2002).

Therefore, with reference to Figures 11 and 12, the findings do not fully support the first hypothesis (illustrated in ***Figure 23***) that the larger the time between two novel stimuli the larger the P300 (H1). In other words, given H1 as it is drawn in ***Figure 23***.A and B, the results show: negative correlated effects in the left hemisphere in control participants, pointing to an unexpected electrical behaviour in ***Figure 23***.C, and a positive correlated novelty effect in frontal and parietal electrodes in schizophrenic patients, pointing to an electrical behaviour in ***Figure 23***.B.

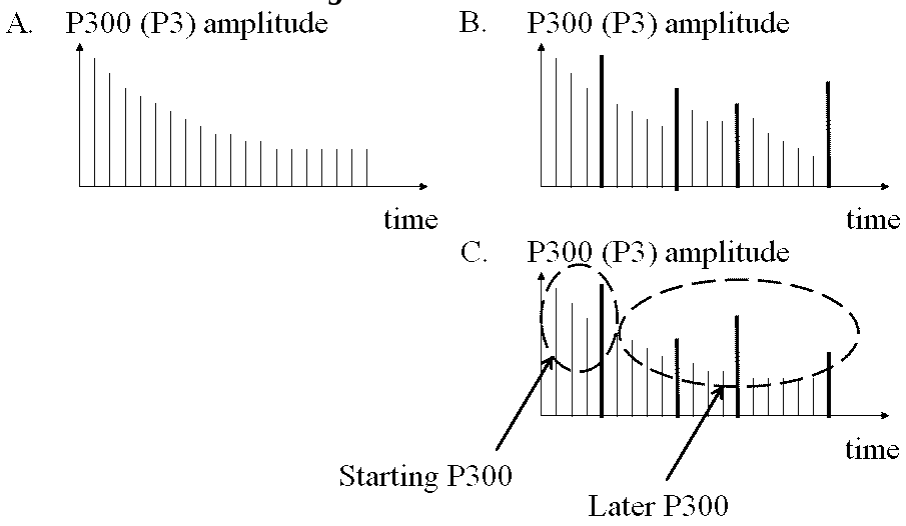


Figure 23 Initial hypothesis plotted with the first results and the route to the sound properties analysis.

A possible explanation is that the four different conditions produce different processing outcomes. In this way, in both groups the P300 response to novel stimulus show different evidence of processing novel and different conditions in: the left hemisphere for the longer the time duration between two NG conditions which suggests the time between conditions is producing an alerting effect in controls. There is also evidence of frontal and parietal electrodes answering positively to the longer time duration between two novel conditions

which suggests prefrontal scalp control and having different parietal electrodes measures and producing reorienting of attention in schizophrenic patients.

Barbalat and colleagues employed structural equation modelling in the participant responses to a letter discrimination paradigm using a first cue as the episodic signal and a contextual signal to decide the finger answer to the task. They found an impairment in the connectivity of the dorsolateral prefrontal cortex for schizophrenic patients (Barbalat et al., 2011). Using functional connectivity for the parietal cortex and the prefrontal cortex (PFC), Tan and colleague's in a N-back memory task, found that connectivity was greater in the schizophrenic patients for ventral PFC and greater in the control group for the dorsal PFC (Tan et al., 2006). Although scalp EEG does not inform about brain source, the results in the present experiment in the Fz electrode, the group differences may be explained by a different interaction of P3 with the inter-stimulus effects which made it difficult to identify a clear pattern of increase or decrease in P3 amplitude as the number of preceding stimuli increase. In addition to that, the control participant at left parietal electrode CP5 and the schizophrenic patient central parietal electrode at Pz electrode may be the subject of reanalysis in other fMRI studies, for example, in Barbalat and colleagues (2011) experiment, parietal regions were not explored.

In addition, in a behavioural experiment using novel sounds in a visual categorization task, Parmentier and colleagues found that behavioural distraction depends on the informational value of the sound changed. They claimed that the low probability of occurrence of a novel sound does not constitute a sufficient condition for behavioural distraction (Parmentier et al., 2010). In this way, it would be inaccurate to assume that an auditory novel event elicits distraction due to its low base rate probability. We showed this in behavioural (alerting and non-facilitative reaction times) and ERP results having stimulus properties correlated with P300 in different Novel properties at different conditions. Our current findings with ERPs

associated with orienting of attention at P3a in the preceding novel condition complement their idea, including the properties of stimulus and condition task switching.

Following the route that the less expected (in time) the stimulus the larger the amplitudes on ERPs (Squires, Wickens, Squires, & Donchin, 1976) we can keep/update that phrase saying that the less expected the stimulus (i.e. differences between the current stimulus and a previous stimulus or by the larger inter stimulus intervals) the larger the ERP amplitudes (see ***Figure 23***). It is important to bear in mind that the previous stimulus properties influences stimulus probability, in the sense that they occur either immediately before or more than 2 trials before, as was shown in ***Figure 22***.

2.4.3 Stimulus sequence effects vs. Stimulus properties (H2)

We found that P3a amplitude showed correlations of different magnitude in the range 0.3- 0.6 depending on whether stimuli were presented to the left or right ear for the different properties based on Sound Duration, Mean Amplitude and Frequency.

A correlation was found between P3a (measured after onset time from 350 to 450 ms) and the durations of previous sound stimuli. However, the results in this experiment show significant correlations with previous sound durations in novel sounds that are linked to the frequency and amplitude of the sounds. Therefore, the second hypothesis is supported for frequency and amplitude but not systematically for duration because of these confounding interactions.

Figure 24 suggest a model that, when the current sound is compared with previous Non-novel sounds, then correlations are strongest in the left hemisphere and when the current trial is preceded by a novel trial then correlations are stronger in the right hemisphere.

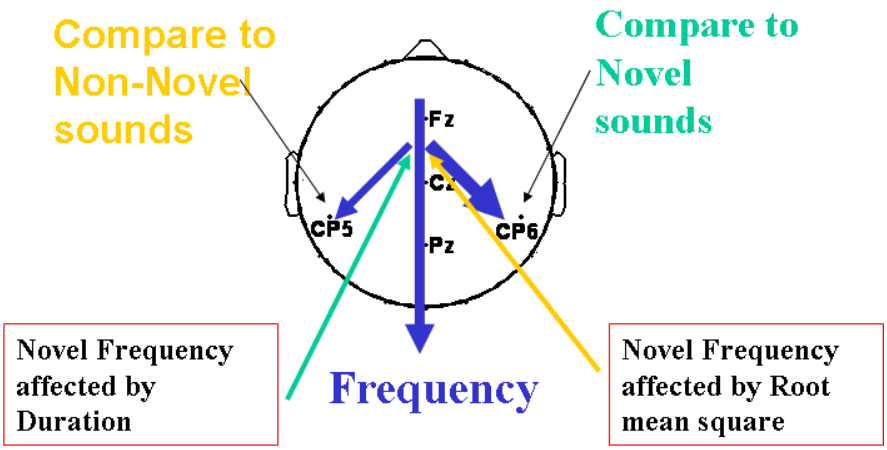


Figure 24 A general route of the sound properties analysis influencing P3a amplitude. Thickness shows strength of the correlations found.

Therefore it would interesting to carry out a further specific experiment whereby novel sounds are changed in duration and ERP waves are analysed under the assumption that novel and non-novel sounds are processed differentially by the two hemispheres. This is explored in chapter 5.

Contextual stimulus properties had significant influences on P3 amplitude in both control and schizophrenic patients. On the one hand, in the control group this is mainly in the stimulus-driven and perception time (0 to 300 ms) between conditions in standard condition. On the other hand, schizophrenic patients show differences in the range of time of gating sounds, P50 either in the first or second stimulus between conditions and within standard condition as well.

Parmentier and colleagues claimed that the advantage of the crossmodal oddball task shows the primordial role of the sound's informational content as demonstrated by the finding of a facilitation of performance by novels when these predicted with certainty the occurrence and timing of targets while standards did not (Parmentier et al., 2010). However, in our purely experimental auditory results, when sound was stripped of its informational value, auditory

novelty had an impact on ERP waves and this indicated that the late brain processes also have the informational content of the previous experience.

Parmentier and colleagues also indicated that behavioural distraction following a novel or deviant sound reflects a delay in the processing of the target, as the consequence of time penalties associated with the shift of attention only operate within the bounds of a goal-relevant stream of auditory events (Parmentier et al., 2010). Our study suggests that in controls, this involves the stimulus-driven network as well. And this can be generalized by any change of either cue or target that would reflect a different brain process.

Parmentier and colleagues suggested that behavioural distraction measured in the cross-modal oddball task is only observed when the irrelevant sound presented to participants provides useful information regarding the upcoming task-relevant stimuli (Parmentier et al., 2010). When stripped of this information, novel sounds produced no distraction. In this study, based on stimulus duration effects, we believe that the properties of the sounds are relevant for the ERP response when the significance of the inter-stimulus properties is changed. Specifically, in the present experiment the interstimulus properties were not significant in several conditions that switch attention in several ways and this shows that stimulus properties are significant information of the upcoming stimuli.

In the general linear modelling approach, the Second Level Analysis based on Two-samples T-test for group comparison reported differences between TNG and NG conditions. The main differences were larger ERP deflection for controls in MMN and P300 for NG condition and smaller in the TNG condition. Also, the R2 values found in the first level analysis and the different regressors found in each condition suggests that the task involves more than simple activation of stimulus-driven and goal-driven attention networks. Limitations: It is important to point out that this analysis has limitations: on the one hand, in the accuracy of connectivity of bins because of the number of channels (32) and the sampling frequency (128 Hz); and on

the other hand, in several frequency properties estimated from the task (detailed results of these calculations are not presented here) as well as in our non-parametric design, which produces variable R2 value distributions across participants. This limitations may result in the smaller correlations measured in some participants..

These sets of regressors coming from both correlation analysis and general linear model in EEG data can be explained taking into account (1) episodic memory; (2) contextual control; or even more significantly (3) attention to details in our attention paradigm design. Limitations: The experiment was carried out with imbalanced group number N = 20 for controls and N = 12 for schizophrenic patients, although LIMO provided a multicomparison this difference limited the comparison between groups.

2.4.4 Effect of the immediately previous trial context on current attention (H3).

In both controls and schizophrenic patients, in section 2.3.5, it was observed that the previous stimulus affects the following standard condition ERP deflections. In the control group, ERP deflections were found mainly in the stimulus-driven and perception time (0 to 350 ms) for S1 and P50 for S2 at NG condition followed by TG condition. On the other hand, in schizophrenic patients deflections are significantly different in gating sounds, P50 either in the first or second stimulus. Models of cognitive dysfunction in schizophrenia patients are frequently discussed as "stimulus-driven" versus "goal-driven" (reviewed by Javitt, 2009), the present findings based on previous trial context suggest that both types of dysfunctions are simultaneously present in schizophrenia extending the view of Leitman (2009) to the temporal scale.Explaining in detail, when the immediately previous context is considered in terms of MMN it was found that the trial pair NG.TG produced a larger MMN, followed by TN.TG and TNG.TG (see ***Figure 25***). Our interpretation is that the novel cause a smaller MMN when the novel is before the cueing effect (TN in dashed and dotted curve) and even less when either is mixed with the goal or having half of the power (TNG in dotted curve).

Therefore, this context-dependent interpretation has two supporting literature findings: (1) it is consistent with the lower amplitude MMN (NG.TG, TN.TG and TNG.TG) or longer latency in MMN peak proposed in a review by Javitt (2000), and (2) it complements results in the case of a sort of different time presentation (300 ms, 1500 ms and 1500 ms respectively adding a 2150 ms for NG.TG) resulting in different sensory deficit in schizophrenia patients in the results of auditory MMN. This may be explained using distributed hierarchical models for deviant stimuli in MMN (Leitman et al., 2009). The results may therefore be consistent with different neurochemical theories of the effects of schizophrenia on MMN, considering NMDA antagonists (Javitt, 2000; Heekeren et al., 2008) and the serotonin receptor (5HT2A) as an agonist giving a model of psychoses that display distinct neurocognitive profiles (Heekeren et al., 2008). Bearing in mind the route for attention and possible network interactions and adding the model for schizophrenia proposed by Ferrarelli and Tononi (2011), it will be interesting to explore techniques as LORETA to study a hierarchical modelling.

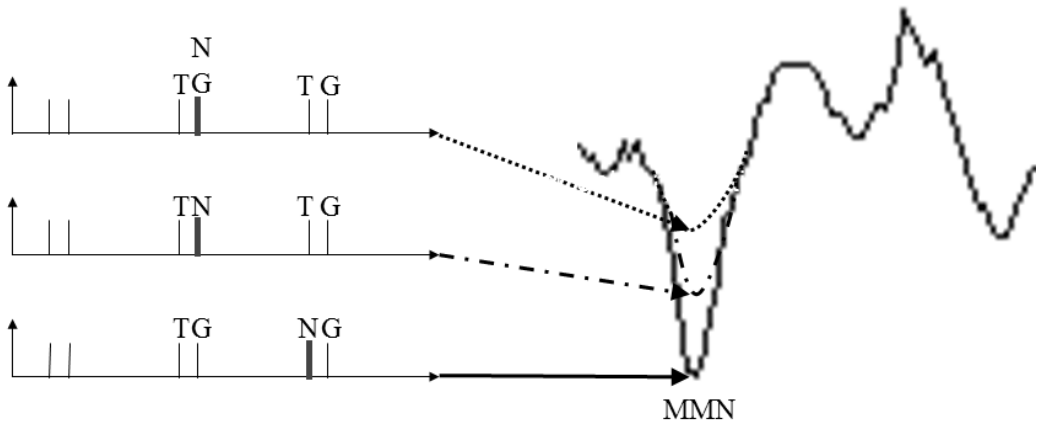


Figure 25 The context interpretation about MisMatch Negativity in schizophrenic patients.

According to Baldeweg and colleagues, frontal and central electrodes should show MMN attenuation (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002). Recently a simulation of an MMN experiment using predictive coding (Friston, 2005) and a again a hierarchical model of

the brain based on relatives changes on the task (Friston, 2008) showed the reduction of MMN in tone repetition in an auditory task (Moran et al., 2013). Our study complements this statement because TN.TG - TG has shown differences across several electrodes in both hemispheres and TNG.TG – TG appears mainly in the right hemisphere in the MMN. These suggest that the Goal stimulus is being processed in the left hemisphere and that attenuates the MMN difference and suppresses P300 differences.

Therefore, with regard to the third hypothesis (H3), H3 is supported and the larger the MMN the larger the P3a, but we also found an effect in time of the novel before the warning signal (S1) in analysis for schizophrenic patients. In this way, when we have the tone as a cue, it is important if the previous sound was a novel or a novel simultaneously with the target. This interpretation suggests that these trial context effects should be explored further to determine whether the time is related with background stimulus for schizophrenic patients. Although scalp EEG does not provide unambiguous information about brain activity sources, this result is consistent with the idea that the frontal lobe (shown in frontal channels) activity generates P3a, having in mind an impairment in processing the stimulus (Uhlhaas & Singer, 2006). In this way, the negative correlation of the distinction of two contiguous stimuli shown in schizophrenic patients at the beginning of section 2.3.5 with stimulus properties can be studied with the progressive MMN reduction showed in this part. Finally this is linked with the studies by Özgürdat and colleagues. They have explored differences between controls, chronic schizophrenics and participants with first episode. Their results pointed to significant differences in those three groups in Pz electrode and the range of time to find the P300 peak was between 280 and 600 ms (Özgürdal et al., 2008). This is consistent with the time property found here, that is first episode participants are developing the time property MMN reduction and consequently a P300 reduction.

Gilmore and colleagues demonstrated that amplitude reduction of P3 in externalizing disorders was not affected by stimulus sequence effects. They found, as expected, that the greater number of standards preceding the target the greater P3 amplitude. Sequence effects in amplitude reduction of P3 were found normal in externalizing disorders and they suggested that such individuals are able to effectively utilize context during the oddball task to form subjective expectancies about the probability of a target occurring (Gilmore, Malone & Iacono, 2012). Limitations: In our study, we found that control and schizophrenic patients show P3 amplitude changes modulated by stimulus properties and contextual effects, but one needs to carefully interpret the present results because of the four conditions presented in the task and the same stimulus sequence for each participant. Therefore a different experiment was developed experimentally in Chapter 4 and optimized in Chapter 5 using randomised trial sequences.

2.4.5 Mutual information is a covariate for schizophrenic patients

In the five channels of analysis (Fz, Cz, Pz, CP6 and CP5), we found that the correlation between P300 and mutual information in the frequency domain, under a cue and orienting mixed auditory paradigm, evokes a right lateralized significant P3 amplitude reduction in schizophrenic patients. With this we have shown that the purely auditory oddball task allows studying informational content. Parmentier and colleagues claimed that in an auditory oddball task, the distracter and the target are embedded into the task and this does not allow the independent manipulation of the distracter's informational content (Parmentier et al., 2010). We can re-state their claim and go further, when the distracter information is shared with the goal, this sharing can control the P300 wave, the biomarker of orienting response. This claim was shown in the schizophrenic patients where the greater the LTAS the greater the P300 response and in the control participants with the LTAS where the correlations considered the left sound lateralisation. As such, it would be interesting to test this for the conflict monitoring task of the experiment, thus in the simultaneous novel and goal condition, and test

if single trial correlation across several channels or a second level analysis in the general lineal model (LIMO) approach would validate or invalidate this informational content argument. Another interesting approach would be to insert novel (S1) followed by the simultaneous novel and target (S2) as fifth condition.

Hughes and colleagues showed that the voice deviants were producing a disruption of the ability to identify the item from a standard set of items. This was reflected in variations in the reaction times as evidence of behavioural distraction to deviant background items (Hughes et al., 2007). These findings were consistent with a previous study where a temporal deviation in Inter-Stimulus Interval (ISI) was used rather than a voice deviation (Hughes, Vachon, & Jones, 2005). These results were interpreted as support for a dual mechanism changing-state and deviation model. In the present experiment, correlations of current preceding novel condition (NG) were tested with the other previous conditions. Several correlations were particularly strong with other previous conditions. One can say therefore that in the cross-modal task, e.g. Parmentier et al. (2010) or Hughes et al. (2005, 2007), auditory distraction can be explained by the nature of the sound and the nature of the processing required in the task. But also, one can say the ISI changes introduces differences in the processing of background stimulus.

From the point of view of the theory of mind in perceptual and attentional processes, the reduced ability to distinguish externally generated stimuli can be reflected by auditory hallucinations. According to Hugdahl, these auditory hallucinations are supported by thalamocortical sensory pathways, from internally generated inputs, which are processed by corticothalamic circuits (Hugdahl, 2009). The contextual effects of previous stimulus properties suggests that P50 gating is different in schizophrenic patients; therefore a strong influence of thalamocortical activation should be implied in this process. The correlations between P300 and S1 durations were stronger in the right hemisphere, consistent with the

right lateralized areas involved in reorienting of attention. In addition, in dichotic listening experiments, it has been shown that patients with schizophrenia have problems reporting the right ear stimulus (Green, Hugdahl, & Mitchell, 1994; Løberg, Jørgensen & Hugdahl, 2004). Therefore, we suggest that the mutual information that appears correlated with P300 amplitude in the stimulus-driven attentional network can reflect a different computation for schizophrenic patients. Assuming that in many schizophrenic patients there is an increased likelihood of auditory hallucination, schizophrenics are said to be in a state of hypervigilance and enhanced stimulus-driven processing to compensate for this impairment.

3 SIMULTANEOUS EEG/fMRI: AN EXPLORATION OF THE PRIOR CONTEXT INFLUENCING BRAIN AREAS ACTIVATED IN AN AUDITORY ATTENTION ORIENTING TASK.

3.1 Introduction

In chapter 2, differences in EEG correlates of goal driven and stimulus driven attention were explored using a distraction paradigm in schizophrenic patients and a control group. A detailed study of stimulus properties and the effects of prior context were shown to be important in modulating the P3a amplitude in the number parity decision paradigm. In the present study, in order to continue the prior context analysis an auditory experiment employing functional Magnetic Resonance Imaging (fMRI) and EEG is analysed.

Prior context in attention has been studied with fMRI in visual tasks. Koechlin and colleagues used an experimental task in which participants were asked to discriminate coloured shapes or letters, or ignore a non-goal stimulus, on the basis of an instruction cue (which initiated each block). On the basis of their hypotheses and their findings, they suggested that the lateral frontal lobes contribute to a cascade of control processes mediating sensory, contextual, and episodic control implemented in premotor, caudal and rostral lateral prefrontal cortical regions, respectively (Koechlin, Ody & Kouneiher, 2003, Koechlin & Summerfield, 2007). Therefore, pending behavioural responses are maintained and managed by prefrontal areas, and the activation of frontal areas can be affected by multitasking. In the 4-condition experiment discussed in Chapter 2, the participants had to maintain a number parity decision goal set while ignoring novel distractors.

The original aim of the experiment described in this chapter was to pilot an auditory attention paradigm with simultaneous EEG and fMRI at 3 T during the technical development phase of the newly installed scanner. These data were collected using a simplified version of the number parity decision paradigm. This study was carried out prior to the analysis described in chapter 2 and this experiment was therefore not informed by the outcome of the previous study. This experiment was carried out as part of a series of tests where participants in the first block were required to lie still in the scanner for 5 minutes (resting state), in a second block they completed a visual working memory (N-Back) task, in a third block they completed 400 trials of the auditory number parity decision task and in the last block they completed a conditioning paradigm. The basic design of the auditory number parity decision task consisted of either a number (goal driven) where participants had to make a forced choice "odd" or "even" response, or a number with a simultaneous laterally presented novel stimulus (goal + stimulus driven) as 'go' trials and either the number zero or novel-only (stimulus driven only) as 'no-go' trials. The original aim of this study was to dissociate activation of the stimulus-driven and goal-driven networks (SDN and GDN) by comparing the hypothesised goal-driven parity decision trials to the hypothesised stimulus-driven distractor trials in the analysis of simultaneous EEG and fMRI data. Preliminary grand averaged ERP waveforms from 5 of 12 participants are illustrated in Figure 1.

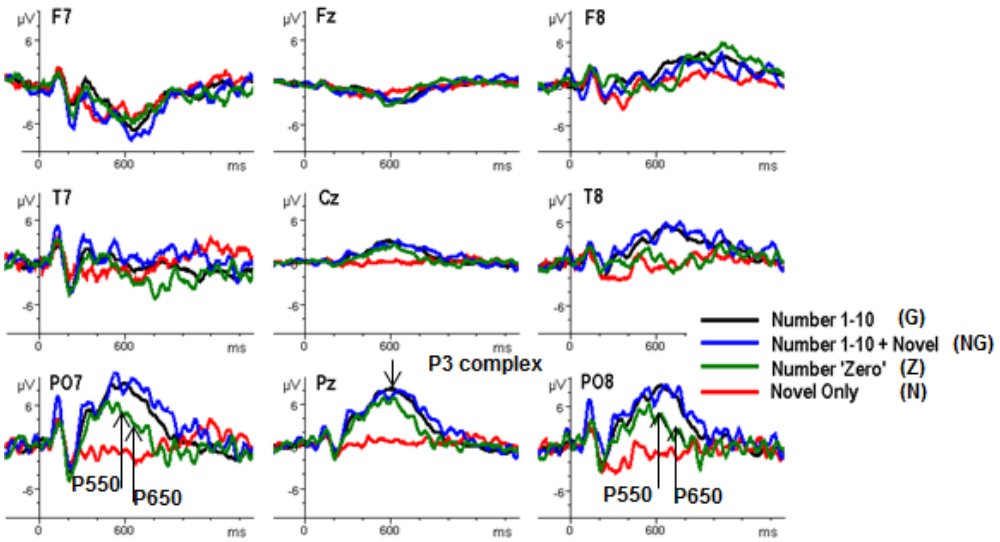


Figure 26 Grand average ERP waveforms for parity decision Goal stimuli (G), simultaneous Novel and Goal stimuli (NG) as well trials on which no response was required, *i.e.* Zero (Z) and Novel (N) stimuli. The P3 complex appears to consist of distinct deflections occurring at 550 and 650 ms. The parietal P550 deflection dissociates on the basis of number versus novel stimuli whereas the P650 deflection dissociates on the basis of response or no response, most clearly at T8. Adapted from Potter et al. (2010).

The preliminary results indicate the presence of several distinct ERP deflections at different electrodes. Right lateralized electrodes (*e.g.*, T8) dissociate 'go' from 'no-go' trials whereas a large positive deflection at ~600 ms at Pz in all the number decision conditions showing an auditory P3 complex. PO7 and PO8 in the no-go 'Zero' condition allow one to differentiate the 'slow wave' associated with behavioural response (P650) from the P3b associated with the resolution of stimulus processing and updating of working memory (P550). In the case of 'Novel Only' stimuli, only a small right lateralized P3a response at ~550 ms was observed (Potter et al. 2010). This last result is consistent with Corbetta and colleagues' argument with regard to the activation of the stimulus-driven part of the attention reorienting network without activation of the goal-driven system and attention orienting (Corbetta et al. 2008). Moreover, exploring the ERP among 5 participants leads to a greater P1 component for simultaneous novel and goal and smaller ERP deflections for novel sounds (Potter et al., 2010).

The aims of the present re-analysis of these data are to determine if the simultaneous EEG and fMRI recordings can provide insights into (1) the effect of the prior stimulus contexts across participants; and (2) explore the sources of the generators of the positive deflections in

the ERP waveforms, including the smaller right lateralised positive deflection observed to novel sounds.

Before describing in detail the analysis of these data, the relevant background literature will be briefly reviewed. Current theories of attention assume the involvement of a distributed control network of areas in stimulus-driven (SDN) selection with the behavioural relevant information (Corbetta & Shulman, 2002). Further, these systems share common areas and interact with the goal-driven (GDN) network (see review of the fronto-parietal visual attention network using single cell recordings in monkeys and fMRI in humans by Kastner & Ungerleider (2000).

Among the multimodal techniques utilised to study the brain, EEG offers high temporal resolution but limited spatial resolution while fMRI offers high spatial resolution but lower temporal resolution. Logothetis and colleagues (2001) carried out seminal work on monkeys with the study of simultaneous intracranial recordings and the blood-oxygen-level-dependent (BOLD) fMRI responses on the visual cortex at 4.7 T. With intracranial recordings the local field potentials (LFP) were obtained. LFP reflects mostly a weighted average of synchronized dendro-somatic components of the input signals of a neural population; therefore the LFP has a similar physiological basis to scalp EEG. Significant correlations (r) between the LFP and the BOLD responses were found, on the one hand $r > .5$ was found at frequencies greater than 15 Hz and, on the other hand, $r < .3$ was found for frequencies smaller than 8 Hz (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). EEG and fMRI can therefore be usefully combined in separate EEG and fMRI recordings with the same experimental design, but also in simultaneous EEG and fMRI recordings (e.g., Debener et a., 2006; De Martino, de Borst, Valente, Goebel & Formisano, 2011). In an auditory oddball task, Horovitz and

colleagues (2002) manipulated the probability of the goal tone using a variable number of non-goal standard tones ranging from 12 to 51 (i.e. local probabilities from 7.69 % to 1.92 %) between consecutive goal tones in a long experiment. The task mainly consisted of non-goal standard tones of 1000 Hz and goal tones of 1500 Hz. They found an increase in P300 amplitude in Pz while BOLD-signal changes increased in the same direction in the SupraMarginal Gyri, Thalamus, insula and right Medial Frontal Gyrus (Horovitz, Skudlarski, & Gore, 2002).

From the ERP deflections: N1 is an earlier deflection and has strong generators in the auditory cortex (Naatanen & Picton, 1987; Picton et al.., 1999). Mulert and colleagues study the activation of temporal, parietal and frontal regions in an auditory oddball task, by recording EEG responses outside as well as inside the scanner (simultaneous EEG/fMRI). The task mainly consisted of non-goal standard tones of 800 Hz and goal tones of 1300 Hz. They reported that although the P300 component was not significantly different when recorded outside or inside the scanner, the N1 component was found to be significantly smaller and of longer latency inside the 1.5 T scanner (Mulert et al. 2004). Consistent with previous results reviewed by Corbetta and Shulman (2002), studies suggest that the target detection (reflected in the P3b component) network comprises the frontal areas, the insula and the temporoparietal junction (TPJ).

Wagner and colleagues used a word goal decision task to find how some tasks are recognized or not in the human brain. The goal was a semantic signal (abstract or concrete) and a nonsemantic signal (upper- or lower-case letter). Results pointed to the lateralisation response for the left prefrontal cortex, left fusiform gyrus and temporal cortices (Wagner et al. 1998).

However, in order to improve and explain how lateralisation activations may be changing in the time course of the study, ERP measures may be carried out.

Few studies have explored the generators of auditory novelty using EEG and fMRI measures. Opitz and colleagues (1999) used a block design in an auditory oddball task, where the goal standard stimulus was a tone of 600 Hz (83.4%), the non-goal deviant stimulus was a tone of 1000 Hz (8.3%) and the non-goal novel stimulus was an environmental sound. They found that novel sounds activated the superior parietal cortex and those subjects showing strong N4 deflections showed an additional right prefrontal cortex (rPFC) activation (Opitz, Mecklinger, Friederici & von Cramon, 1999). Bearing in mind the distributed areas for attention (Corbetta & Shulman, 2002), Strobel and colleagues (2008) aimed to improve Opitz and colleagues (1999) study using simultaneous EEG/fMRI recordings with an event related design in an auditory oddball task. They used tones of 350 and 650 Hz and environmental sounds where participants were required to silently count standard tones as targets in 50% of the cases and novel sounds as targets in the other 50%. They found that the bilateral superior temporal and right inferior frontal areas showed strongest activation with novel sounds (Strobel et al., 2008).

Kiehl and colleagues used fMRI to study the brain areas activated in an auditory oddball task seeking to answer whether gender influences the magnitude or distribution of brain activity associated with the P3a and P3b responses. They implemented a task in which the standard tone stimulus had a probability of 0.8, the target tone stimulus had a probability of 0.1 and the novel stimuli had a probability of 0.1 with an Inter Trial Interval (ITI) of 2000 ms. They examined hemodynamic fMRI studies of target detection and novel stimulus processing in five groups of 20 subjects. They did not find evidence of a gender effect, but this study is

relevant to the present research because it was an oddball task, and the ITI was similar. We used a single sound per trial and gender was imbalanced. They found around 28 brain areas for the target over the standard stimulus (the superior parts of the left PreCentral Gyrus, left middle and Inferior Frontal Gyrus, and brainstem), 20 brain areas for the novel over the non-goal standard tone stimulus (bilateral Amygdala, Anterior and Posterior Cingulate, bilateral inferior parietal lobe, and brainstem), 29 brain areas for the target over the novel stimulus (bilateral middle Frontal Gyrus, right Inferior Frontal Gyrus, left PreCentral and postcentral Gyrus, and right Cerebellum) and 29 brain areas for the target over the novel stimulus (bilateral middle Frontal Gyrus, bilateral middle Temporal Gyrus, and right precentral Gyrus and additional regions in left middle frontal Gyrus, right middle temporal Gyrus, and left angular Gyrus and Precuneus) (Kiehl et al., 2005). Therefore, in terms of comparison we should expect to find several areas activated for the four switching conditions.

Based on the findings of the literature summarized above and the results presented in chapter 2, the following hypotheses were drawn:

H1: The participants must orient their attention in response to novel distractors and this should be associated with bilateral activations of the goal-driven system. This would confirm the sensitivity of the task in the framework of the distributed control of attention proposed by Corbetta and colleagues (Corbetta & Shulmann 2002; Corbetta et al., 2008).

H2: Bearing in mind the contextual effect of the immediately previous trial, in a task with several conditions (Koechlin et al., 2003, 2007), several significant different brain areas should appear in different fMRI contrasts. Therefore based on Koechlin's findings and our results in the experiment with 4 conditions in Chapter 2, the Goal-driven experiment should produce significant modulations of activations in memory areas as a result of modulation by

different areas of the prefrontal cortex, dependent of the level of contextually based executive controls outlined by Koechlin et al. (2003, 2007). The differing contextual conditions associated with the different experimental conditions will activate different prefrontal areas for Novel followed by the Goal (N.G), simultaneous Novel and Goal followed by the Goal (NG.G) and Zero followed by the Goal (Z.G) i.e. different prefrontal activations should be found in Z.G vs. G.G, N.G vs. G.G, NG.G vs. Z.G, NG.G vs. G.G, and N.G vs. Z.G contrasts.

3.2 Methods

Participants

Twelve adults participated in the present study (mean age: 30.75 ± 8.8 years; range 18–48 years). All subjects self-reported normal hearing and no history of known neurological illness. All participants consented to participate in the study. One healthy participant was excluded because the structural MRI was lost, leaving 11 healthy (10 right handed and 1 left handed) subjects.

Experiment Design

Subjects were asked to perform an odd/even auditory number decision task during simultaneous scalp EEG and fMRI recordings. The paradigm was composed of 400 trials, with trials chosen pseudo-randomly from one of four different conditions. Each trial consisted of a sound stimulus. The parameters of the stimuli are given in table 5. Participants were asked to respond by pressing a button as quickly as possible without sacrificing accuracy. Participants used the index and middle fingers of their right hand. The Inter-Trial Interval (ITI) was between 1900 and 2100 ms. Figure 1 shows the ITI and its variability across event timing during the task. As demonstrated in Figure 1, ITI variability was homogenous and there is no evidence of possible order effects in the task design, which

means that single trial analysis can be performed on the data. The task was presented in one single block (400 trials) with each of the four conditions presented in random order. Stimulus sequence was the same across all participants.

Stimuli

Stimuli were sounds presented using Nordic Neurolab Electrostatic Headphones at 80 dB sound pressure level. Sound files were stereo with 16 bit resolution and 22050 Hz sampling rate.

In the standard goal stimulus condition (G), the stimulus (S2) was a number of 300 ms duration. In the non-goal stimulus condition (Z), S2 was the number zero of 300 ms duration. In the novel only condition (N), S2 was a novel sound of 55, 135 or 200 ms duration. Finally, in the simultaneous novel and goal condition (NG), S2 was a number of 300 ms duration simultaneously presented with a lateralized novel sound of 100 ms duration.

Table 5

Stimuli combinations for the simultaneous EEG/fMRI experiment.

Stimuli name	Number of presentations	Code Processed	Stimuli S2	
			Type	*Time*
Standard goal stimuli	250	G	Number	300 ms
Non-goal stimuli	50	Z	Zero	200 ms
Simultaneous novel and goal	50	NG	Number + Novel	300 ms
Novel stimuli	50	N	Novel	55, 135, 200 ms

EEG Recording

EEG data were recorded continuously using a 64-channel EEG acquisition system designed especially for the MR environment (Vision Recorder, Brain Product, Inc., Munich, Germany). The electrode placement followed the extended international 10–20 system, using

FCz as a reference electrode. Amplified signals were digitized at 5000 Hz with a 16-bit resolution. All electrode impedances were < 20 kΩ. Data were band-pass filtered between 0.016–250 Hz during data acquisition. Trials with excessive peak-to-peak deflections, amplifier clipping or excessive high frequency (EMG) activity were excluded before analysis.

EEG Data Analysis

Pre-processing was conducted first using Analyzer software (Brain Vision, LLC). MR artifacts were corrected using an artifact template based on 30 volume acquisitions with a further low pass filter at 70 Hz and sampling frequency was downsampled to 256 Hz. The cardioballistic artifact was corrected using a template based approach. Data were then exported to EEGLAB and eye blinks and other artifacts were rejected using ICA.

In the introduction, preliminary analysis demonstrated the presence of identifiable ERPs (Potter et al., 2010). For this experiment, the G condition has 250 trials and the other 3 conditions have 50 each one, this reduces the noise near to root square of 250 (≈ 15.8) in the G condition and similarly around ≈ 7.1 in the other 3 conditions. We were then confronted with the problem of finding reliable single trial ERPs, because of having too few participants (n = 5) in Potter's analysis or all participants (n = 12) in the recordings of the present study. These numbers result in a reduction of the noise in the few participants around ≈ 2.2 or a reduction of ≈ 3.5 in the all participants. This noise reduction is added to the high electrical noise on the EEG recordings induced by the high magnetic field of the scanner. Furthermore, these noises affected the processing of the cardioballistic rejection. To be able to know whether we can resolve this problem, the EEG recordings were filtered with a low-pass at 70 Hz. Subsequently, raw EEG data and filtered EEG data were compared to find out whether the quality of noise on the EEG recordings was sufficiently reduced. Following the above

procedures, EEG data were analyzed using EEGLAB (Delorme & Makeig, 2004) and Matlab in-house scripts. Eye-movements and artifacts were removed using an independent components analysis (ICA). Data was then filtered using a high-pass filter at 0.75 Hz and epoched from 300 ms before stimulus onset to 900 ms after stimulus onset. A baseline correction was then applied. Epochs were then checked for trials with excessive peak-to-peak deflections, amplifier clipping, or other artifacts. The EEG signal was then analysed in a single participant to determine whether the data were of sufficient quality to produce single trial averages across-participants. Because of the poor quality of the EEG data, the calculation of sound properties and P300 peaks followed by bootstrapped correlations and False Discovery Rate was not used.

fMRI Acquisition and analysis

Whole-brain images (30 slices; 2.6 mm thick, 0.4 mm gap, 64×64 pixels in-plane resolution, overall resolution 3.75×3.75×5 mm) were collected on a 3 T Trio Siemens scanner using an echo-planar imaging sequence. Scans were acquired with a repetition time of 2.5 s and echo time of 30 ms. Additionally, a T1-weighted structural scan was acquired for each subject (1 mm isotropic resolution). SPM8 was used for both pre-processing and statistical analysis (Friston, 2004). Images were spatially realigned to reduce movement artifacts. Mean image and structural data were used for co-registration, and co-registration results were then used to produce normalized images. Images were spatially normalized to the MNI template and spatially smoothed using a Gaussian kernel of 8 mm full-width at half height. The BOLD signal was then high-pass filtered with a cut-off of 256 s.

A subset of different possible regressors was used: (1) from initial conditions; (2) extended contextual conditions (see Figure 27). To explore the main effects of conditions and contextual analysis in the whole group, we adopted a voxel-wise type I error threshold of $\alpha =$

0.03 and used the cluster extent method to correct for multiple comparisons (Slotnick, Moo, Segal & Hart, 2003). Areas exceeding a corrected cluster-wise type I error threshold of α = 0.006 (k > 1055 voxels, equivalent in spatial extent to 15 original non-resampled voxels) were selected for further analysis to determine the directionality of category-specific main effects and to test for interactions. Given that the cluster extent method is not as stringent as false discovery rate (FDR) or family wise error (FWE), we have chosen α = 0.03. With these 1055 voxels the second level random effects analyses were conducted. These analyses were achieved by entering the six covariate images of interest into one-group *t*-test. Due to the small number of participants for orienting (n = 6) and non-orienting (n = 5), only statistical analysis within 'distracted' participants (n = 6) and the whole (n = 11) groups was carried out.

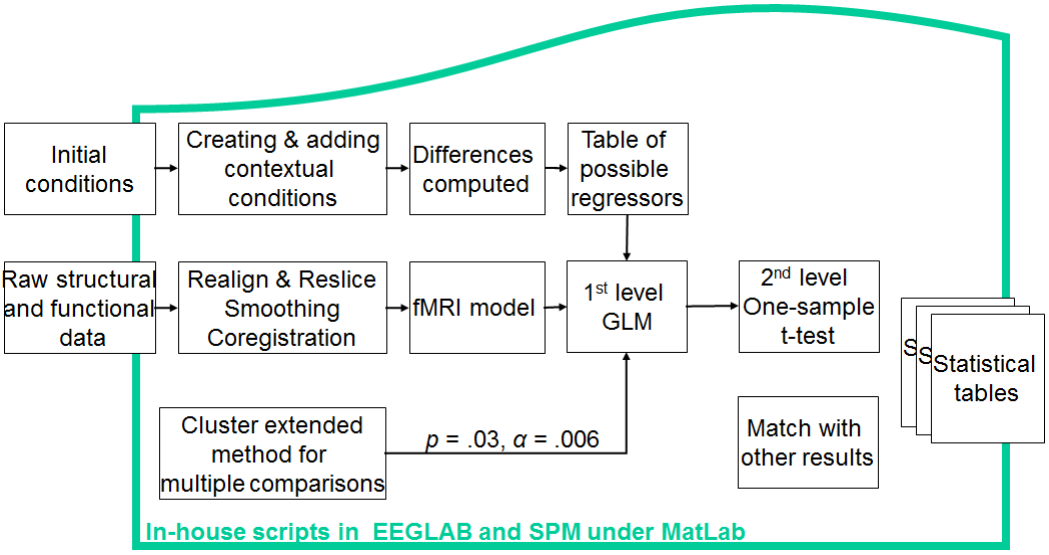


Figure 27. Preprocessing and analysis diagram used for the auditory oddball task in the simultaneous EEG and fMRI recording.

3.3 Results

3.3.1 Behavioural Results

Both accuracy and mean response latencies were examined in the critical trials common to our two goal stimulus conditions, Goal (G) and the simultaneous Novel and Goal (NG).

Overall, participants performed well (94% accuracy of goal trials). The proportion of correct responses was analyzed using a 2 way ANOVA. The main effect of condition was not significant across subjects ($F(1,11) = 0.43$, $p = .5136$).

A time series analysis using a running average of reaction times was conducted in each participant to explore the basis of these non-significant results and the small effect size (< .01). Running average reaction times in the 12 control participants for conditions G (coloured in black) and NG (coloured in gray) are illustrated in *Figure 28*.

Solid lines in the upper plots are the means for every condition (black for standard Goal stimuli, gray for the simultaneous Novel and Goal). In the bottom plots the difference of the RTs between the G condition minus the NG condition are shown. There the average and standard deviation calculation of reaction times was run, taking as the centre, the central trial plus and minus 75 trials (condition G) or 15 trials (condition NG) across the whole of the possible accurately answered trials (this explains why the measure does not start from 0 and finish at 400) rendering 151 trials (condition G) and 31 trials (condition NG). This is called running average of Reaction time or running average RT.

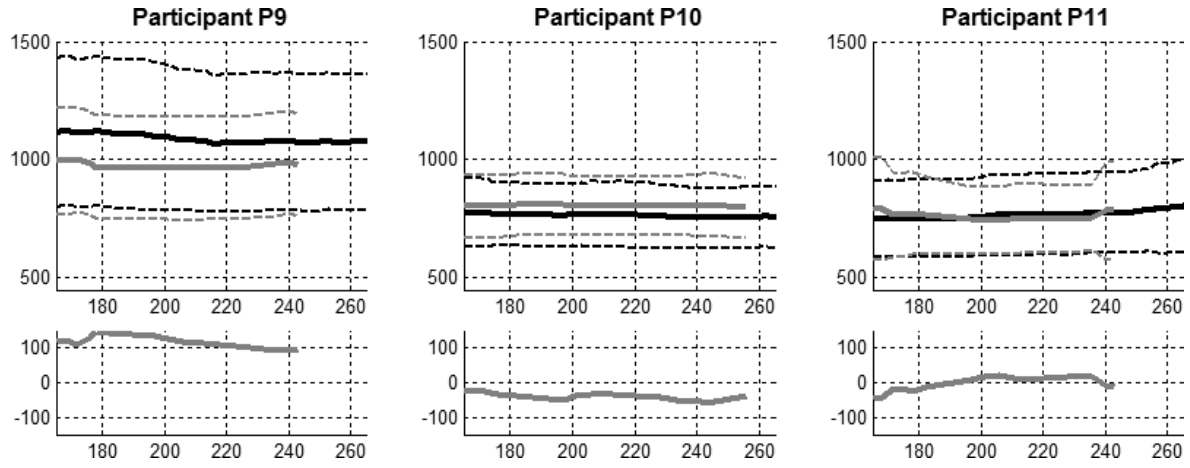


Figure 28 Running average of RT for conditions G (coloured in black) and NG (coloured in gray) in the 12 participants. Solid lines in the upper plots are the means at every condition

(black for standard target condition and gray for noisy target). In the bottom plots the difference of the RTs between G and NG is shown.

Novel distractors slowed reaction times in participants 7, 8, 10, 14, 15 & 16, speeded up reaction times in participants 4, 5, 9 & 12 while participants 6 and 11 show no differences. In *Figure 28* the running average RTs for the G and NG conditions are illustrated along with the average difference between the two conditions.

Overall, the lack of significant differences in RT in the 2 way ANOVA may be explained by the individual differences in pattern of the running average reaction times in the different conditions. Some individuals clearly show distraction effects while others do not.

3.3.2 EEG Results

EEG comparison between the raw EEG signals and the filtered signals at 70 Hz were carried out for all the participants. To enable comparison, the EEG difference was plotted with threshold amplitude of 300 uV (10 times the expected maximum P300, *i.e.* 10 x 30 uV). Noise amplitude was calculated as the maximum amplitude of the 400 ms period after the stimulus (S2) was presented.

Figure 29 shows in the participant TD04 a specific example of the variability in time of the noise generated by the recording system. For example, channels F1 and F2 are affected and noise is changing with time, while other channels such as Fz and Cz are not affected in the scale of 300 uV. Moreover, more than 200 trials did show problems of active auditory signals over electrodes. On the other hand, *Figure 30* in the participant TD05 shows a specific example of the variability in time of the noise generated only in some electrodes by the

recording system. For example, channels T7, T8, CP5, TP10 and C1 are affected and noise is changing with time, while other channels such as Cz and Pz are not significantly affected in the scale of 300 uV. In addition, the signals on channels Fz and AF4 are greater than 300 uV in amplitude in all trials. Moreover, 65 trials (of 400 trials) did showed problems of active auditory signals over electrodes.

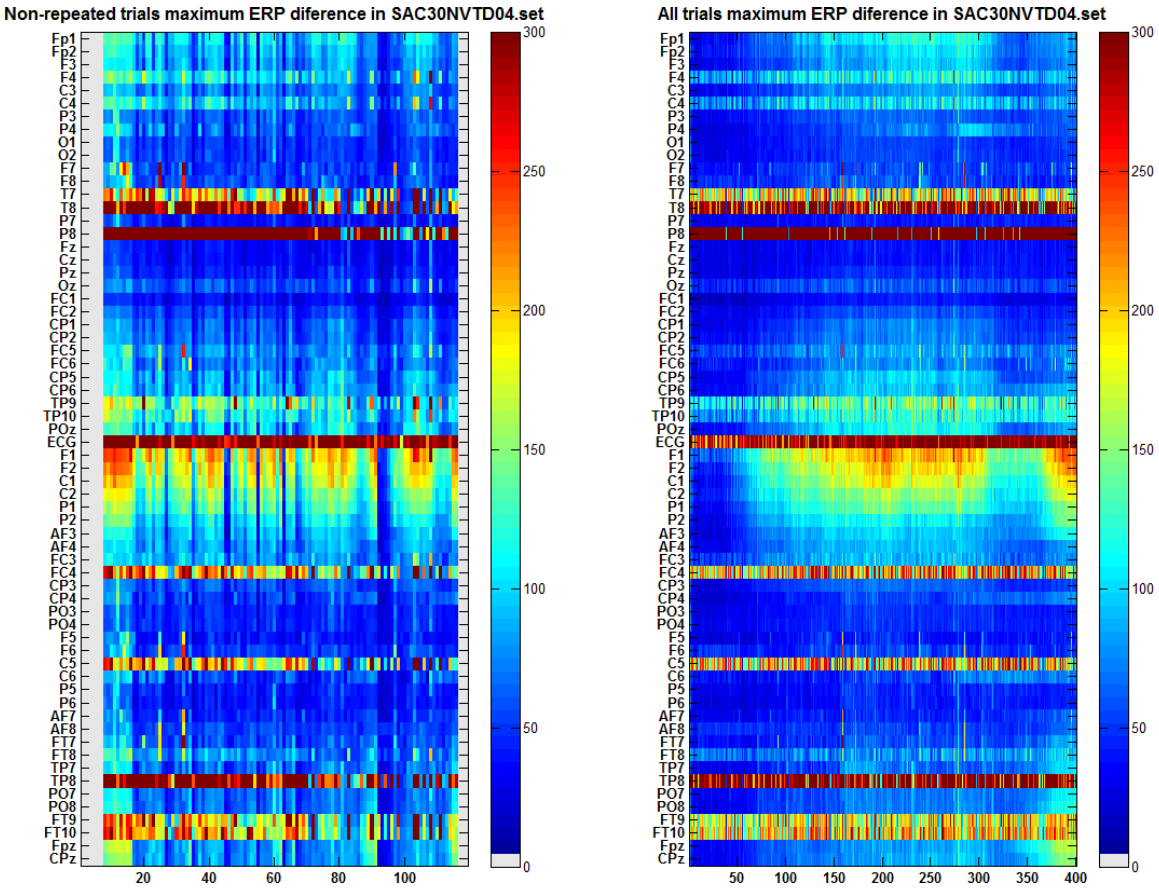


Figure 29 Time difference of maximum EEG difference between the amplitudes of filtered and raw EEG data across channels from 0 to 400 ms after auditory onset stimulus in the participant labelled with fMRI04. On the left: trials grouped by codes. First numbers from 0 to 10 are shown, and later Novel events are shown. On the right: successive 400 trials.

Our results showed that the noise was either (1) strong and localized in some electrodes changing slowly over time or (2) almost all electrodes were initially noise-free up to some point in time when variations in noise were increasing for many of the electrodes.

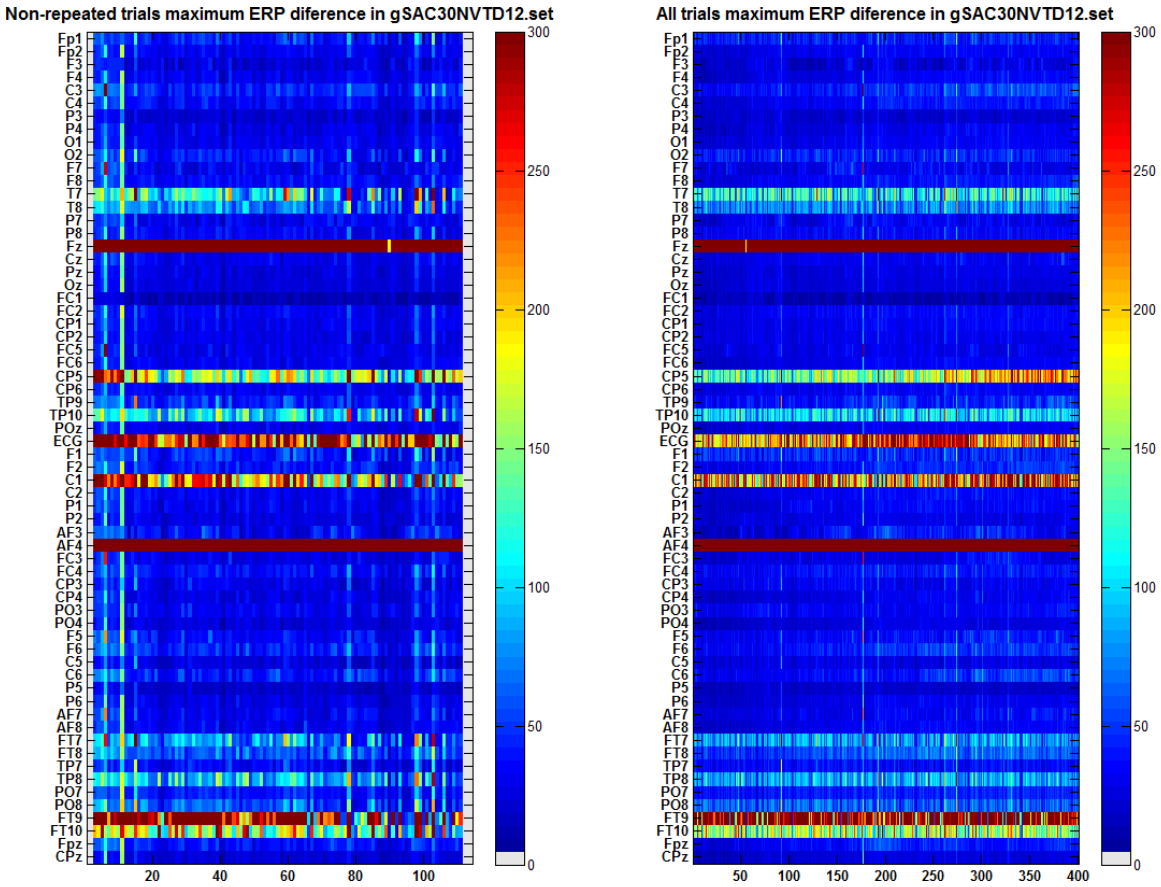


Figure 30 Channel noise of maximum EEG difference between the amplitudes of filtered and raw EEG data across channels from 0 to 400 ms after auditory onset stimulus in the participant labelled with fMRI12. On the left: trials grouped by codes. First numbers from 0 to 10 are shown and later Novel events are shown. On the right: successive 400 trials.

After the analysis of the different EEG datasets and cardiobalistic rejection the data were epoched for one of the clearest datasets of the 12 participants at electrodes Cz and Pz (TD05).

In this single subject EEG data (TD05), a further cardioballistic rejection was run and grand average ERPs were computed. The grand average ERPs relative differences are shown in *Figure 31*. It can be seen that after artifact removal there is limited evidence of an ERP. Although it was expected that ERPs in channels Cz and Pz would be evident (along other channels, i.e. F7 and T7), there are no clear differences between condition in Cz and Pz and possibly novel noise introduce a different spectral content (see first 300 ms in Fz channel).

Therefore, this data processing was not good enough to proceed further with the single trial EEG analysis across all participants for the purpose of predicting fMRI signal fluctuations. After cardioballistic correction and artifact rejection using ICA the EEG was averaged. ERP plots indicated that there was insufficient good signal for single trial analysis and it was decided not to proceed further with the single trial EEG analysis across all participants or attempt to use this information as a predictor in the fMRI analysis.

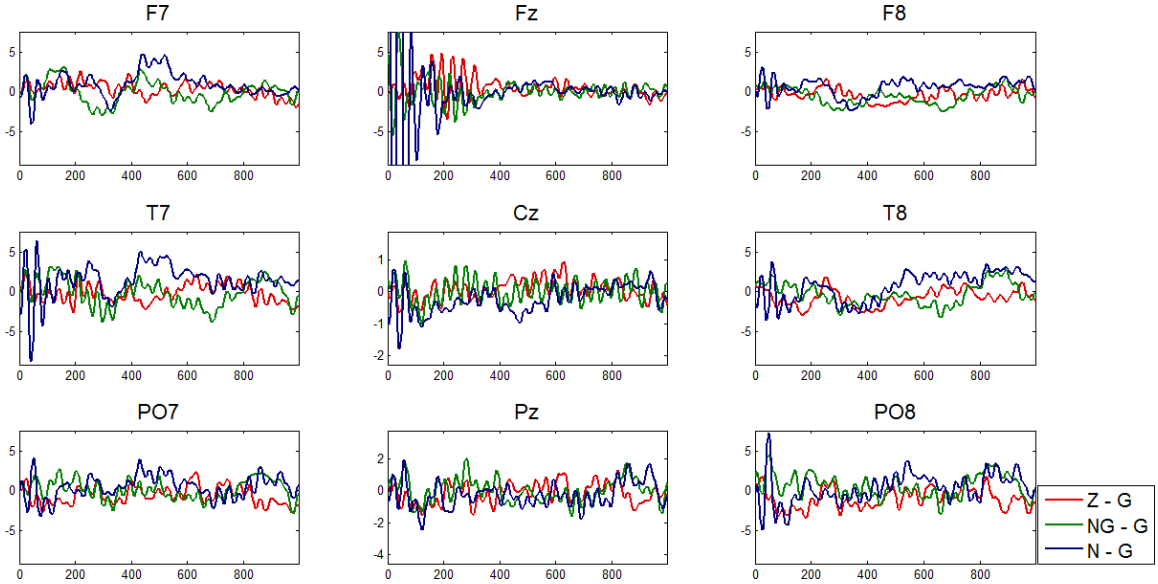


Figure 31 Subtraction of the ERPs of the standard Goal stimuli from the Zero, simultaneous Novel and Goal, and Novel stimuli in few electrodes. Note that the amplitude scales in Cz and Pz are respectively four and two times that scales in the other electrodes.

Because of the difficulties of the noise levels in the EEG datasets it seemed impractical to attempt single trial averaging across participants and it was decided to analyse the fMRI data independently. No further analysis of the EEG was therefore attempted.

3.3.3 fMRI contrasts

The purpose of this experiment was to determine if the slowing of responses to simultaneous number and novel stimuli (NG) was associated with the activation of the stimulus driven attention network without activation of the goal driven system. The Novel only condition (N)

was introduced to allow visualisation of an attention orienting response, assumed to involve activation of the stimulus and goal driven systems but also involving withholding a button press. The zero (Z) condition was introduced in an attempt to visualise the effects of withholding a response in the novel condition.

When the classical contrasts between N, Z, NG conditions and the G condition were carried out in all the participants, most of the N vs G constrast did not showed relatively different activation and as well as the NG vs G did not showed ventral areas with relatively different activation (detailed results of these analyses are not presented here). Therefore, these relatively different activations in all the participants were not supporting Corbetta and Shulman SDN and GDN in a cortical network for control of attention. In this way, the detailed analysis is presented for the behavioural 'distracted' participants (n = 6). Tables 6 to 8 list the brain areas and their equivalent Brodmann Areas (BA) activated when the N, NG, and Z conditions were contrasted with the Goal (G) condition.

First, *Figure 32* and Table 6 show and list the contrast between Zero (Z) and Goal (G) conditions, respectively. According to the results, there is no support for any brain areas activated with both positive and negative contrasts and also with different BAs. Both hemispheres in frontal, temporal and occipital areas showed differences, while in the parietal lobe only the left hemisphere showed significant differences. The Left and Right Superior Temporal Gyrus (R STG) showed differences and also the Right Superior Frontal Gyrus (R SFG), which is consistent with the stimulus-driven control proposed by Corbetta and colleagues in 2002; these differences are positively biased to the Z condition. On the other hand, although there were no differences in the Inferior Parietal Lobule (IPL), there are no differences in the left and right Brodmann Area 8 (Frontal Eye Field, FEF) and the expected different activation for IPs is not shown. Therefore, the brain areas do not show clearly the goal-driven control of attention proposed by Corbetta and colleagues in 2002, but these brain

areas are consistent with the different frontal activity in BA 6 hypothesized for response inhibition in Go/No Go tasks (Simmonds, Pekar, & Mostofsky, 2008).

On the other hand, the primary motor area and the Precentral Gyrus in BAs 4 and 6 (in the left and right hemisphere) exhibited significant positive activation biased to the Z condition (see Table 6). This supports the hypothesis of different motor area activation due to the high Goal probability (62.5 %) over the Zero probability (12.5 %). Moreover, the Caudate Tail and Right Fusiform Gyrus (BA 37) are activated particularly in the G condition and this suggests a visual activation going from the lower part Temporal Lobe, which can be explained by a projection from the Caudate Tail to the Superior Colliculus, and allows visual information to evoke saccadic eye movements (Sato & Hikosaka, 2002) and it is found stronger for high-value objects (Hikosaka, Yamamoto, Yasuda & Kim, 2013) and that possibly activates the Right Fusiform Gyrus.

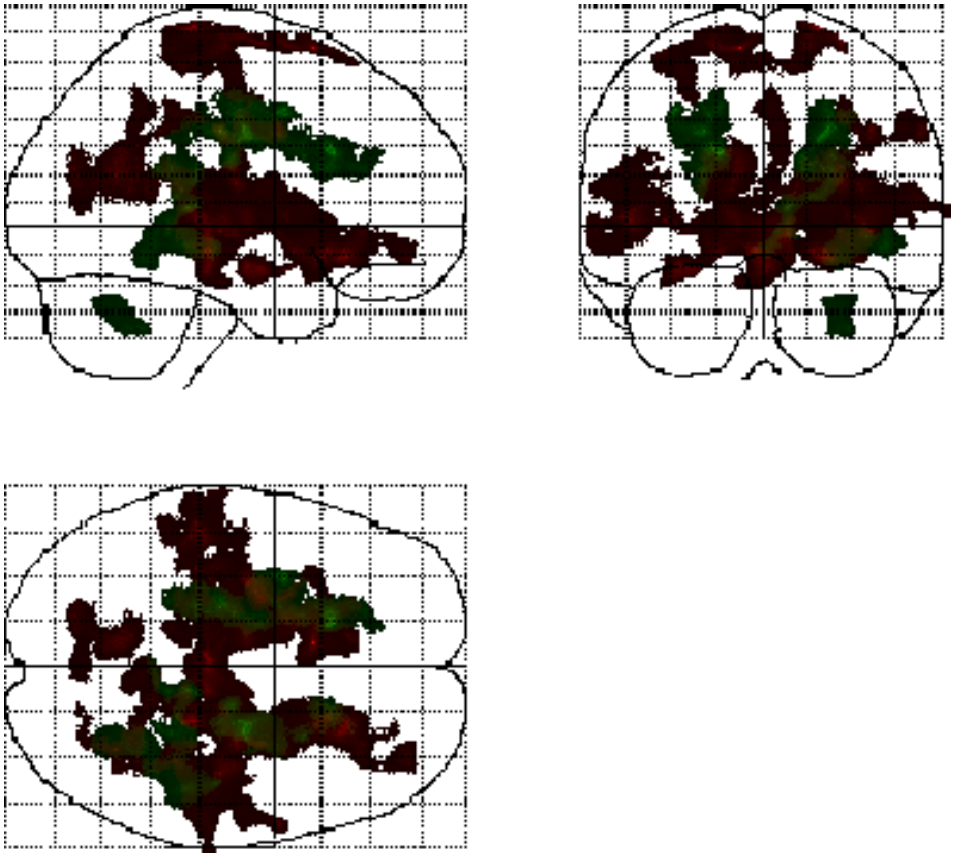


Figure 32 Glass brain regions for the T-test comparison Zero (Z) versus goal (G) conditions. Red are positive T-values, Green are negative T-values and Yellow are both negative and positive overlapping.

Table 6

Brain areas and statistical results of Orienting Group (n = 6) with p < .03 (uncorrected) and 1055 voxels activated for Zero vs Goal conditions: Z vs G

Significant brain areas activated Positive difference	Voxels with maximum T *Positive*		*Coordinates*			Brodmann areas
	T	*p*	*x*	*y*	*z*	
Frontal lobes						
1 L MedialFrontal Gyrus	5.12	.002	-3	-25	58	6
2 L MiddleFrontal Gyrus	3.87	.006	-28	-11	46	6
3 L ParacentralLobule	3.23	.012	-2	-29	59	6
4 L PostcentralGyrus	4.08	.005	-16	-34	62	4
5 L PrecentralGyrus	6.46	<.001	-37	-19	61	4,6
6 L SuperiorFrontal Gyrus	78.71	<.001	-8	18	61	6
7 R MiddleFrontal Gyrus	3.71	.007	30	8	60	6
8 R ParacentralLobule	6.49	<.001	10	-29	57	6
9 R PostcentralGyrus	3.21	.012	17	-34	59	4
10 R PrecentralGyrus	10.76	<.001	57	3	32	4,6
11 R SuperiorFrontal Gyrus	12.99	<.001	29	-2	64	6
Parietal lobes						
12 L PostcentralGyrus	5.02	.002	-15	-36	64	3
13 L Precuneus	8.02	<.001	-17	-72	24	31
14 R PostcentralGyrus	3.50	.009	17	-37	59	3,4
Temporal lobes						
15 R SuperiorTemporal Gyrus	10.17	<.001	37	-32	15	22,41
Occipital lobes						
16 L Cuneus	7.90	<.001	-17	-72	21	18
17 L Precuneus	6.08	<.001	-20	-72	18	31
Limbic Lobe						
18 L CingulateGyrus	9.12	<.001	-9	-54	26	31
19 L ParahippocampalGyrus	10.69	<.001	-26	3	-14	34
20 L ParahippocampalGyrus Amygdala	15.46	<.001	-26	-5	-12	
21 L PosteriorCingulate	12.10	<.001	-9	-56	25	31
22 R CingulateGyrus	5.02	.002	5	-47	39	31
Deep gray (Sub lobar areas)						
23 L LentiformNucleusPutamen	10.00	<.001	-16	6	-8	31
24 L Thalamus	9.23	<.001	-9	-9	1	34
25 L ThalamusVentral LateralNucleus	9.11	<.001	-10	-9	3	
26 R Claustrum	10.04	<.001	37	-15	-2	31
27 R Thalamus	12.04	<.001	10	-24	0	31
Additional regions						
28 R MidbrainSubstania Nigra	6.89	<.001	11	-22	-7	

Significant brain areas activated Negative difference	Voxels with maximum T *Negative*		*Coordinates*			Brodmann areas
	T	*p*	*x*	*y*	*z*	
Frontal lobes						
Parietal lobes						
Temporal lobes						
1 R CaudateCaudateTail	2.77	.019	35	-32	0	
Occipital lobes						
2 R FusiformGyrus	6.38	<.001	28	-48	-7	37
Limbic Lobe						
3 R ParahippocampalGyrus	5.28	.002	30	-45	-9	19,37
Deep gray (Sub lobar areas)						
4 L Insula	4.12	.005	-29	-32	21	13
5 R CaudateCaudate Tail	5.84	.001	22	-32	14	
6 R ThalamusPulvinar	12.87	<.001	10	-28	9	
Additional regions						
7 L Anterior LobeCulmen	2.96	.016	-2	-44	-5	
8 R Anterior LobeCulmen	6.49	<.001	1	-43	-5	
9 R Anterior Lobe	7.32	<.001	32	-53	-29	
10 R Posterior LobeCerebellarTonsil	4.06	.005	26	-56	-31	
11 R Posterior LobeDeclive	4.06	.005	27	-60	-22	
12 R Posterior LobePyramis	4.19	.004	29	-57	-27	

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

The results of the contrasts between Novel (N) and Goal (G) conditions are shown on Table 7. Both hemispheres in frontal, temporal and limbic brain areas showed differences, while in the temporal lobe only the left hemisphere showed a difference, whereas in the parietal lobe only the right hemisphere showed significant differences. According to the results, only the Right STG in the BA 22 is activated with both positive and negative contrasts. Also, the Right Precentral Gyrus, Right SFG and the Right STG are activated with positive and negative contrasts but in different Brodmann Areas (see highlighted results in Table 7). The STG showed positive differences in the Left (BA 6) and Right (BA 6). The Left Inferior Frontal Gyrus (IFG) in BA 47 and Right IFG (BA 47) showed positive differences and other parts of the Right IFG showed negative differences. The Right IPL showed negative differences (BA 40). The Right Middle Frontal Gyrus (MFG) showed negative differences (BA 4). The Left and Right STG showed positive differences while the Right STG showed negative differences, which is consistent with regions involved in the stimulus-driven control network proposed by Corbetta and Shulman in 2002 and part of the reorienting network proposed by Corbetta and colleagues in 2008. There are also negative differences observed in the IPL (BA 40), which is consistent with Krall and colleagues' interpretation of the function of the anterior R TPJ function in attention to Corbetta's model (Krall et al. 2014). On the other hand, no differences were observed in the Brodmann Area 8 (FEF). Therefore having no clear activations in the IPs (sought in BA 7, 19, 39 and 40), there is no clear evidence of differences in the goal-driven control of attention proposed by Corbetta & Shulman in 2002. The involvement of the GDN and SDN for the orienting response in the hypothesis H1 has been supported for the stimulus-driven network.

Bearing in mind the result of the other contrasts, these positive and negative differences in the frontal, parietal and temporal lobes will be considered in the discussion. The high Goal

probability (62.5 %) over the Novel probability (12.5 %), produced activations in the primary motor area and the Precentral Gyrus (in the left and right hemisphere) exhibited significant positive activation dorsally biased (BA 4) to the N condition and ventrally biased (BA 43) to the G condition (see Table 7). Therefore, the different motor activation of hypothesis H5 is visualized when Goal and Novel only conditions are contrasted.

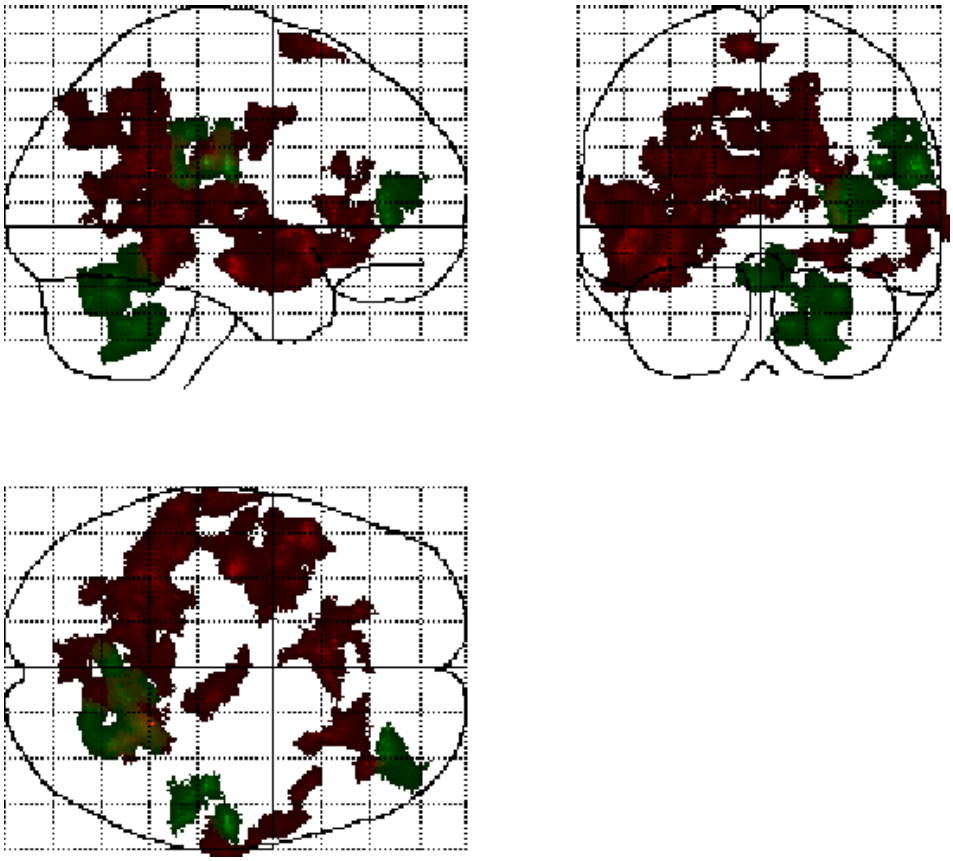


Figure 33 Glass brain regions for the T-test comparison Novel (N) versus goal (G) conditions. Red are positive T-values, Green are negative T-values and Yellow are both negative and positive overlapping.

Table 7

Brain areas and statistical results of Orienting Group (n = 6) with p < .03 and 1055 voxels activated for Novel vs Goal conditions: N vs G

Significant brain areas activated Positive difference	Voxels with maximum T value Positive		Coordinates			Brodmann areas
	T value	p value	x	y	z	
Frontal Lobes						
1 L InferiorFrontal Gyrus	5.02	.002	-43	14	-7	47
2 L SuperiorFrontal Gyrus	14.84	<.001	-5	21	61	6
3 **R InferiorFrontal Gyrus**	4.11	.005	27	30	-7	47
4 R ParacentralLobule	8.56	<.001	19	-42	54	5
5 **R PrecentralGyrus**	5.23	.002	62	-5	10	43
6 **R SuperiorFrontal Gyrus**	2.84	.018	6	21	62	6
Parietal Lobes						
7 R Precuneus	11.93	<.001	20	-46	35	31
Temporal Lobes						
8 L MiddleTemporal Gyrus	13.91	<.001	-59	-33	4	21,22
9 L Sub Gyral	11.18	<.001	-40	-14	-9	21
10 L SuperiorTemporal Gyrus	19.34	<.001	-48	12	-8	22,38,41,42
11 L TransverseTemporal Gyrus	8.51	<.001	-63	-13	13	42
12 R MiddleTemporal Gyrus	3.54	.008	58	-2	-4	21
13 **R SuperiorTemporal Gyrus**	9.11	<.001	67	-15	9	**22**,38,42
14 R TransverseTemporal Gyrus	4.80	.002	66	-16	11	41,42
Limbic Lobe						
15 L AnteriorCingulate	3.85	.006	-5	34	19	24,32
16 L CingulateGyrus	3.61	.008	-2	-9	31	24
17 L ParahippocampalGyrus	14.93	<.001	-36	-45	-6	19,37
18 R AnteriorCingulate	3.22	.012	12	32	-10	32
19 R CingulateGyrus	4.44	.003	6	-17	32	23
Deep gray (Sub lobar areas)						
20 L CaudateCaudate Head	6.14	<.001	-13	22	1	
21 L Extra Nuclear	3.58	.008	-36	13	-10	13
22 L Insula	16.82	<.001	-44	4	-2	13
23 R ThalamusPulvinar	4.07	.005	13	-29	13	
Additional regions						

Significant brain areas activated Negative difference	Voxels with maximum T value Negative		Coordinates			Brodmann areas
	T value	p value	x	y	z	
Frontal Lobes						
1 **RInferiorFrontal Gyrus**	2.45	.028	40	51	2	
2 RMiddleFrontal Gyrus	4.27	.004	36	45	10	10,46
3 **RPrecentralGyrus**	3.05	.014	58	-17	35	4
4 **RSuperiorFrontal Gyrus**	2.78	.019	37	56	15	10
Parietal Lobes						
5 R InferiorParietal Lobule	10.40	<.001	56	-33	23	40
6 R PostcentralGyrus	10.70	<.001	49	-28	35	2,3
Temporal Lobes						
7 **R SuperiorTemporal Gyrus**	3.93	.006	52	-33	17	**22**,41
Limbic Lobe						
Deep gray (Sub lobar areas)						
8 R Insula	8.09	<.001	56	-33	20	
Additional regions						
9 L Anterior LobeCulmen	3.70	.007	0	-60	-10	
10 R Anterior LobeCerebellarLingual	4.63	.003	8	-48	-16	
11 R Anterior LobeCulmen	6.71	<.001	28	-57	-21	
12 R Anterior Lobe	9.17	<.001	22	-49	-29	
13 R Anterior LobeDentate	5.11	.002	20	-50	-25	
14 R Anterior LobeNodule	8.50	<.001	12	-54	-28	
15 L Posterior LobeDeclive	9.54	<.001	-3	-59	-15	
16 R Posterior LobeCerebellarTonsil	7.10	<.001	29	-56	-33	
17 R Posterior LobeDeclive	9.91	<.001	17	-67	-19	
18 R Posterior LobeUvula	3.54	.008	23	-67	-24	13

Anatomical labels and associated p statistical values are listed. T scores from the omnibus analyses of 6 participants for each ROI are presented.

A

The contrasts between simultaneous Novel and Goal (NG) and Goal (G) conditions are shown on Table 8. Both hemispheres in frontal, temporal, parietal, occipital and limbic brain areas showed differences. According to the analysis, only the Right Medial Temporal Gyrus in the BA 10 and the Right Cingulate Gyrus in the BA 24 are activated in both positive and negative contrasts (see highlighted results in Table 8). Also the Right Precentral Gyrus, the Right SFG, the Right STG, and the Right Anterior Cingulate Cortex have activations in positive and negative contrasts but in different Brodmann Areas. Brain differences are biased to the NG condition in the Left STG, in the Left and Right IFG, and the Left and Right Medial Frontal Gyrus, which is consistent with stimulus-driven control proposed by Corbetta & Shulman in 2002. Also important for hypothesis H1 are the differences in activation in the Right IPL, which is consistent with goal-driven control proposed by Corbetta & Shulman in 2002, although this is biased for the Goal condition. Therefore, the additional activation of the SDN has not been found in G vs NG conditions. However, it is important to remember that these participants showed slower reaction times in the NG condition, in part due to the effect of orienting response matched with conflict monitoring. In this way, considering the activation of both sides of the Anterior Cingulate Cortex in positive and negative contrasts (Table 8), this matches with areas of activation observed in conflict monitoring (Weissman, Giesbrecht, Song, Mangun & Woldorff, 2003). This is addressed in the discussion along with the other contrasts.

Also, the primary motor area, the Precentral Gyrus (in both hemispheres) was found significant different between G and NG conditions (see Table 8). On the left hemisphere was biased frontally to NG condition and on the right hemisphere was biased to G condition. This supporting the idea of the different motor area activation due to that the high Goal probability (62.5 %) over the simultaneous Novel and Goal probability (12.5 %).

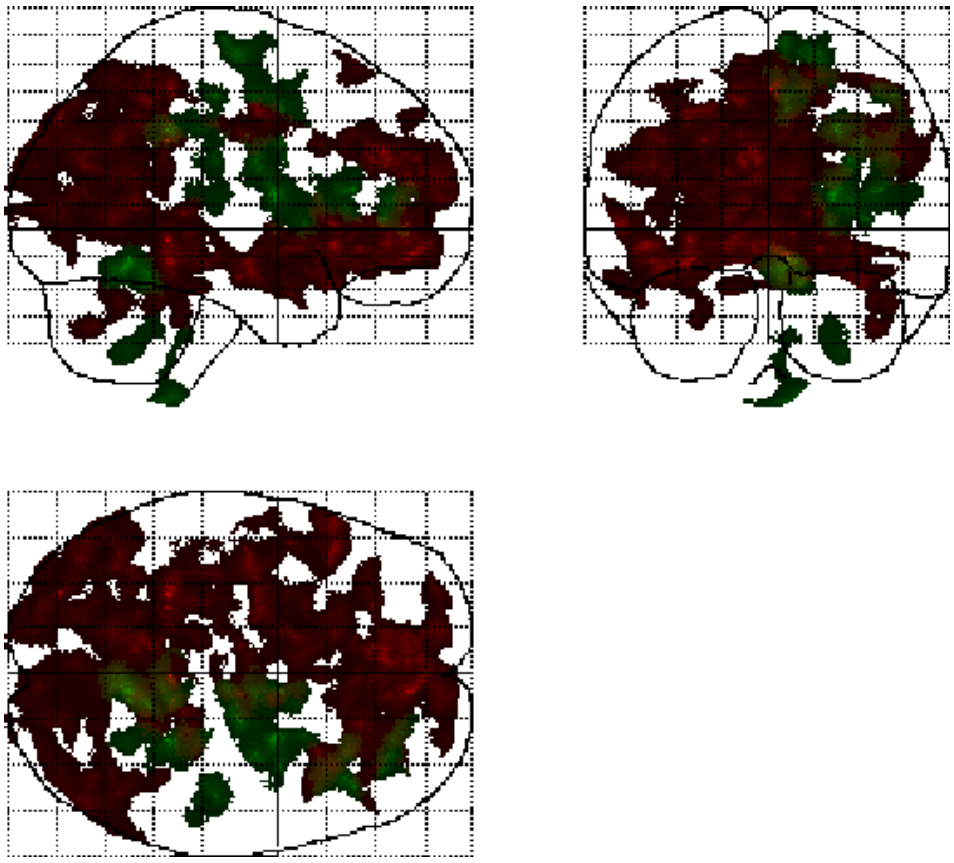


Figure 34 Glass brain regions for the T-test comparison the simultaneous Novel and Goal (NG) versus the Goal (G) conditions. Red are positive T-values, Green are negative T-values and Yellow are both negative and positive overlapping

Table 8

Brain areas and statistical results of Orienting Group (n = 6) with p < .03 (uncorrected) and 1055 voxels activated for simultaneous Novel and Goal vs Goal conditions : NG vs

	Significant brain areas activated Positive difference	Voxels with maximum T *Positive*		*Coordinates*			*Brodmann areas*
		T	*p*	*x*	*y*	*z*	
	Frontal lobes						
1	L InferiorFrontal Gyrus	16.69	<.001	-53	19	2	45,47
2	**L MedialFrontal Gyrus**	30.06	<.001	-9	40	20	10,9
3	L MiddleFrontal Gyrus	19.09	<.001	-25	33	-14	11
4	L PrecentralGyrus	4.61	.003	-35	-2	39	6
5	L SuperiorFrontal Gyrus	11.58	<.001	-31	58	15	10,6,8,9
6	**R MedialFrontal Gyrus**	**21.43**	<.001	5	50	-10	**10**
7	R ParacentralLobule	23.20	<.001	3	-36	52	5
8	**R SuperiorFrontal Gyrus**	3.75	.007	3	31	49	8
	Parietal lobes						
9	L Precuneus	28.17	<.001	-30	-77	42	19,7
10	R AngularGyrus	15.78	<.001	48	-68	31	39
11	R Precuneus	12.14	<.001	16	-45	55	7
	Temporal lobes						
12	L MiddleTemporal Gyrus	15.77	<.001	-48	3	-20	21
13	L Sub Gyral	19.03	<.001	-43	-11	-10	21
14	L SuperiorTemporal Gyrus	9.77	<.001	-38	-53	23	39
15	R FusiformGyrus	4.95	.002	46	-58	-18	37
16	R Sub GyralHippocampus	7.45	<.001	29	-30	-6	
	Occipital lobes						
17	L Cuneus	10.15	<.001	-15	-86	25	18,19
18	R Cuneus	9.89	<.001	5	-84	36	17,19
	Limbic Lobe						
19	L AnteriorCingulate	30.46	<.001	-9	36	21	32
20	L CingulateGyrus	10.44	<.001	-6	34	27	24,32
21	L ParahippocampalGyrus	34.40	<.001	-28	-39	-7	36,37
22	L PosteriorCingulate	8.77	<.001	-16	-58	9	30
23	**R AnteriorCingulate**	10.48	<.001	3	26	-4	24
24	**R CingulateGyrus**	**8.98**	<.001	7	-47	39	**24**,31
25	R ParahippocampalGyrus	5.22	.002	20	-30	-8	30,35,36
	Deep gray (Sub lobar areas)						
26	L LentiformNucleusLateralGlobus Pal	12.66	<.001	-15	2	-6	
27	L LentiformNucleusPutamen	14.47	<.001	-14	6	-6	
28	R LentiformNucleusMedialGlobus Pa	11.87	<.001	10	-2	-1	
29	R Thalamus	3.07	.014	21	-33	8	
30	R ThalamusPulvinar	9.82	<.001	14	-30	7	
	Additional regions						
31	**L Anterior LobeCulmen**	7.13	<.001	-16	-34	-18	
32	**R Anterior LobeCulmen**	12.98	<.001	12	-39	-12	
33	**R Posterior LobeDeclive**	6.34	<.001	45	-57	-20	
34	R Posterior LobeTuber	8.94	<.001	42	-69	-28	

	Significant brain areas activated Negative difference	Voxels with maximum T *Negative*		*Coordinates*			*Brodmann areas*
		T	*p*	*x*	*y*	*z*	
	Frontal lobes						
1	**L MedialFrontal Gyrus**	2.86	.018	-2	-5	53	6
2	R CingulateGyrus	4.46	.003	5	12	37	32
3	R InferiorFrontal Gyrus	3.46	.009	43	19	11	45
4	**R MedialFrontal Gyrus**	**9.44**	<.001	5	-16	65	**10**,32,6
5	R MiddleFrontal Gyrus	9.95	<.001	19	-10	58	46,6
6	R PrecentralGyrus	5.09	.002	43	14	9	4,44,6
7	R Sub Gyral	3.88	.006	18	-6	56	6
8	**R SuperiorFrontal Gyrus**	6.45	<.001	8	-16	66	6
	Parietal lobes						
9	R InferiorParietal Lobule	2.90	.017	50	-29	24	40
10	R PostcentralGyrus	5.07	.002	40	-21	46	2,3
	Temporal lobes						
11	R SuperiorTemporal Gyrus	3.58	.008	45	-20	9	13,41
12	R TransverseTemporal Gyrus	4.36	.004	45	-20	12	41
	Occipital lobes						
	Limbic Lobe						
13	**R AnteriorCingulate**	3.39	.01	18	44	7	32
14	**R CingulateGyrus**	**12.85**	<.001	8	4	41	**24**,32
	Deep gray (Sub lobar areas)						
15	R Claustrum	6.70	<.001	29	-1	15	
16	R Insula	5.82	.001	37	18	8	13,40
17	R LentiformNucleusPutamen	24.27	<.001	24	0	12	
	Additional regions						
18	**L Anterior LobeCulmen**	6.94	<.001	-1	-59	-10	
19	R Anterior LobeCerebellarLingual	4.24	.004	8	-48	-16	
20	**R Anterior LobeCulmen**	22.97	<.001	7	-54	-7	
21	R Anterior LobeCulmenof Vermis	6.55	<.001	2	-63	-10	
22	R Anterior Lobe	3.95	.005	23	-48	-29	
23	R Posterior LobeCerebellarTonsil	5.60	.001	28	-55	-35	
24	**R Posterior LobeDeclive**	12.13	<.001	4	-60	-12	

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

3.3.4 fMRI results based on the immediately preceding context analysis included in the analysis for 'distracted' participants.

Continuing with the focus of the condition of the trial immediately prior to the current trial as suggested in chapter 2, the classical fMRI analysis was extended. The contextual cases tested in this analysis are: Z.G vs. G.G, N.G vs. G.G, NG.G vs. Z.G, NG.G vs. G.G, and N.G vs. Z.G.

Common different brain area activations are in the Left Parietal Precuneus, the Right Sub lobar Insula and in the Right Temporal Lobe in the Superior Temporal Gyrus (R STG). In the last case, L STG has different brain activation except for the N.G vs. Z.G contrast (this is discussed in section 3.4.3).

Table 9 lists the differences observed in the contrast between Z.G and G.G. Both hemispheres in frontal, temporal, parietal, occipital and limbic brain areas showed differences strongly biased to the Z.G contextual condition. According to the results, there are no brain areas with the same BA in the positive and negative contrasts, and only the Left Medial Frontal Gyrus with different Brodmann Areas (BA), BA 6 biased to Z.G and the BA 9 biased to the G.G condition. The left and right frontal areas in Inferior- and Middle Frontal Gyrus (IFG and MFG) are positive activated. Also positive differences were found for R MFG, R IFG, and R IPL, and L IPs and R IPs.

Table 9

Brain areas and statistical results of Orienting Group (n = 6) with p < .03 (uncorrected) and 1055 voxels activated for Zero followed by the Goal and Goal followed by the Goal conditions : Z.G vs G.G

Significant brain areas activated Positive difference	Voxels with maximum T value *Positive*		*Coordinates*			*Brodmann areas*
	T	*p*	*x*	*y*	*z*	
Frontal lobes						
1 L MedialFrontal Gyrus	5.26	.002	-1	-24	59	6
2 L ParacentralLobule	2.71	.021	-2	-29	59	6
3 R InferiorFrontal Gyrus	14.80	< .001	23	28	-10	47
4 R MedialFrontal Gyrus	3.66	.007	4	-26	58	6
5 R MiddleFrontal Gyrus	22.96	< .001	24	26	-11	11
6 R ParacentralLobule	5.76	.001	10	-29	57	3,31,5,6
7 R PostcentralGyrus	3.88	.006	17	-34	61	4
8 R PrecentralGyrus	4.83	.002	18	-15	66	4,6
9 R SuperiorFrontal Gyrus	5.36	.002	28	-7	66	6
Parietal lobes						
10 L PostcentralGyrus	3.22	.012	-57	-27	19	40
11 L Precuneus	7.89	< .001	-18	-73	23	31
12 R AngularGyrus	7.43	< .001	50	-68	34	39
13 R InferiorParietal Lobule	7.42	< .001	54	-58	40	39,40
14 R PostcentralGyrus	3.76	.007	13	-34	63	3
15 R Precuneus	4.12	.005	44	-71	41	19,39
Temporal lobes						
16 L MiddleTemporal Gyrus	7.71	< .001	-60	-30	2	19,21,22,39
17 L SuperiorTemporal Gyrus	10.07	< .001	-50	-31	3	21,22,41,42
18 L TransverseTemporal Gyrus	5.80	.001	-41	-32	11	41
19 R MiddleTemporal Gyrus	3.83	.006	46	-63	27	39
20 R SuperiorTemporal Gyrus	5.86	.001	38	-55	17	13,22,41,42
21 R TransverseTemporal Gyrus	3.49	.009	51	-24	10	41
Occipital lobes						
22 L Cuneus	15.58	< .001	-15	-79	27	18,19,7
23 L Precuneus	9.50	< .001	-19	-77	28	31
24 L SuperiorOccipital Gyrus	5.27	.002	-35	-83	29	19
25 R MiddleTemporal Gyrus	7.69	< .001	39	-58	16	19
26 R Precuneus	3.97	.005	14	-72	26	31
Limbic lobes						
27 L CingulateGyrus	6.94	< .001	-10	-55	28	31
28 L PosteriorCingulate	11.93	< .001	-6	-57	25	31
29 L Precuneus	4.98	.002	-12	-43	37	31

Significant brain areas activated Negative difference	Voxels with maximum T value *Negative*		*Coordinates*			*Brodmann areas*
	T value	*p value*	*x*	*y*	*z*	
Frontal lobes						
1 L MedialFrontal Gyrus	4.47	0.0033	-12	39	23	9
Parietal lobes						
Temporal lobes						
Occipital lobes						
2 R FusiformGyrus	5.35	0.0015	28	-48	-7	37
3 R ParahippocampalGyrus	4.96	0.0021	26	-48	-9	37
Limbic lobes						
4 L AnteriorCingulate	3.38	0.0098	-12	36	24	32
5 R ParahippocampalGyrus	3.80	0.0063	31	-47	-6	19

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

Table 9 (continued)

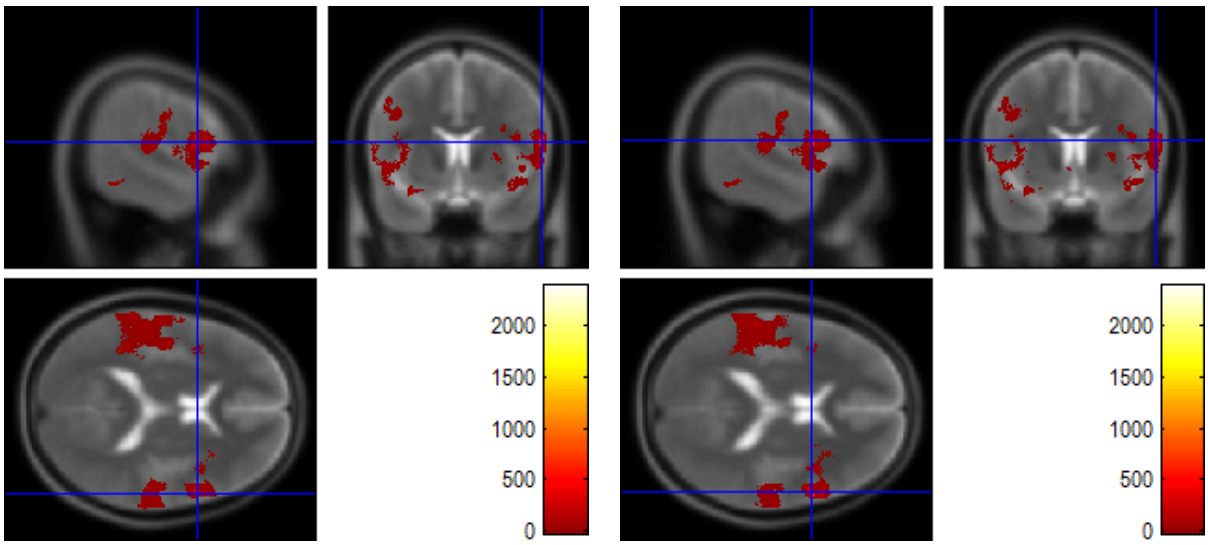
Brain areas and statistical results of Orienting Group (n = 6) with p < .03 (uncorrected) and 1055 voxels activated for Zero followed by the Goal and Goal followed by the Goal

Significant brain areas activated Positive difference	Voxels with maximum T value *Positive*		*Coordinates*			*Brodmann areas*	Significant brain areas activated Negative difference	Voxels with maximum T value *Negative*		*Coordinates*			*Brodmann areas*
	T	*p*	*x*	*y*	*z*			*T value*	*p value*	*x*	*y*	*z*	
Deep gray (Sub lobar areas)							*Deep gray (Sub lobar areas)*						
30 L LentiformNucleus	3.04	.014	-15	-5	4		6 R ThalamusPulvinar	6.94	0.0005	9	-30	9	
31 L LentiformNucleusLateralGlobus Pallidu	4.02	.005	-14	0	1								
32 L LentiformNucleusMedialGlobus Pallidu	3.59	.008	-11	0	-1								
33 L LentiformNucleusPutamen	3.36	.01	-18	1	3								
34 L Thalamus	6.25	< .001	-9	-9	1								
35 L ThalamusMammillary Body	3.16	.012	-13	-20	2								
36 L ThalamusMedial DorsalNucleus	4.15	.004	-7	-20	3								
37 L ThalamusVentral AnteriorNucleus	3.19	.012	-16	-8	12								
38 L ThalamusVentral LateralNucleus	6.74	< .001	-10	-9	3								
39 L ThalamusVentral PosteriorLateral Nucl	2.96	.016	-17	-22	1								
40 L ThalamusVentral PosteriorMedial Nucl	3.24	.011	-14	-21	0								
41 R Claustrum	6.28	< .001	36	-19	4								
42 R Insula	5.14	.002	41	-18	4	13							
43 R LentiformNucleusPutamen	4.37	.004	24	1	14								
44 R Thalamus	19.51	< .001	10	-24	0								
45 L MidbrainSubstania Nigra	5.64	.001	-14	-21	-6		7 L Anterior LobeCulmen	2.94	0.016	-1	-46	-6	
46 R MidbrainRed Nucleus	3.58	.008	8	-20	-6		8 R Anterior LobeCulmen	3.65	0.0074	2	-44	-5	
47 R MidbrainSubstania Nigra	4.06	.005	11	-22	-7								

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

Table 10 lists the differences observed in the contrast of sequences N.G and G.G. Both hemispheres in frontal, temporal, parietal and right limbic brain areas showed differences strongly biased to the N.G contextual condition. According to the results, there are no common areas for positive and negative contrast. There are strong frontal differences in R Precentral Gyrus and the R IFG and in 5 other frontal areas. Results showed that the greatest differences measured occurred towards the most frontal area of the brain, with the greatest frontal differences measuring up to 37 mm in the left MFG and up to 28 mm in the right MFG, which means that frontal activation is larger in the left hemisphere when the Novel is presented immediately before the present Goal stimulus. This left lateralisation response is consistent with the present Goal stimulus .

Moreover, the PreCentral Gyrus is activated differently between this N.G and G.G contrast, with a clearly right lateralized bias. Bearing in mind that this area was not found in the results for the N and G contrast, thus the Novel before a Goal makes more contribution to different motor area activations. Therefore, this result suggests that attention to the task by the participants produces different motor control in N vs. G contrast and in N.G and G.G contrast. This is addressed in the discussion. Overall these differences in the Prefrontal Cortex by the trial before the G condition in analysis support hypothesis H2.



Strongest contrast in the Right Precentral Gyrus [58 8 12] Strong contrast in the Right Inferior Frontral Gyrus [58 7 16]

Figure 35 Brain regions for the contrast between sequences N.G and G.G as conditions. A) Cross sectional images with the blue cross bars point to the maximum F value in the Left Left Medial Frontal Gyrus at MNI voxel [58 8 12]. B) Cross sectional images with the blue cross bars point to a local maximum F value in the Left Precuneus in the parietal lobe at MNI voxel [58 7 16].

Table 10

Brain areas and statistical results of 'distracted' subgroup (n = 6) with p < .03 and 1055 voxels activated for Novel and Goal Stimulus vs Goal and Goal conditions: N.G vs G.G

Significant brain areas activated	Voxels with maximum T value					Brodmann
Positive difference	*Statistics*		*Coordinates*			areas
	T	*p*	*x*	*y*	*z*	
Frontal lobes						
1 L InferiorFrontal Gyrus	14.38	< .001	-42	13	-7	47
2 L MiddleFrontal Gyrus	29.22	< .001	-24	37	-8	11,47,6
3 L PrecentralGyrus	14.09	< .001	-39	-18	41	4
4 L SubcallosalGyrus	4.95	.002	-19	15	-11	47
5 R CingulateGyrus	6.62	< .001	15	14	37	32
6 R InferiorFrontal Gyrus	37.42	< .001	57	8	14	44,47,6,9
7 R MedialFrontal Gyrus	3.26	.011	10	28	30	6,9
8 R MiddleFrontal Gyrus	16.43	< .001	53	6	34	6,8,9
9 R PrecentralGyrus	48.74	< .001	58	8	12	4,44,6
Parietal lobes						
10 L InferiorParietal Lobule	21.01	< .001	-64	-24	28	40
11 L PostcentralGyrus	35.14	< .001	-61	-21	28	2
12 L Precuneus	19.25	< .001	-13	-56	51	7
13 R InferiorParietal Lobule	9.72	< .001	66	-34	30	40
14 R PostcentralGyrus	5.15	.002	57	-22	43	2,3
15 R Precuneus	15.35	< .001	18	-58	55	7
Temporal lobes						
16 L FusiformGyrus	18.68	< .001	-33	-41	-16	20
17 L InferiorTemporal Gyrus	15.19	< .001	-56	-9	-16	21
18 L Sub Gyral	15.58	< .001	-39	-12	-8	21
19 L SuperiorTemporal Gyrus	20.46	< .001	-48	6	-3	22,38
20 R MiddleTemporal Gyrus	4.67	.003	59	-60	11	37,39
21 R SuperiorTemporal Gyrus	7.05	< .001	64	-40	21	13,22,42
Limbic lobes						
22 R CingulateGyrus	15.48	< .001	16	-27	39	24,31,32,9
Deep gray (Sub lobar areas)						
23 L CaudateCaudate Head	2.46	.028	-11	15	-6	
24 L Insula	27.92	< .001	-52	-34	19	13
25 L LentiformNucleusMedialGlobus Pallidu	13.90	< .001	-15	-4	-3	
26 L LentiformNucleusPutamen	3.49	.009	-19	12	-7	
27 R Insula	17.34	< .001	42	12	13	13
Additional regions						
28 L Anterior LobeCulmen	14.93	< .001	-24	-40	-17	
29 R Anterior LobeCulmen	16.67	< .001	12	-60	-10	
30 R Anterior Lobe	3.19	.012	11	-42	-27	
31 R Posterior LobeCerebellarTonsil	3.93	.006	6	-47	-33	
32 R Posterior LobeDeclive	22.13	< .001	12	-62	-11	
Positive difference						
Limbic lobes						
1 R AnteriorCingulate	4.23	.004	5	19	19	6, 33
Additional regions						
2 L Caudate Body	7.89	< .001	-9	17	13	2

Anatomical labels and associated T statistical values are listed. T scores from the omnibus analyses of 6 participants for each ROI are presented.

Table 11 lists the observed differences for the contrast of sequences N.G and NG.G, showing frontal differences in 10 regions. Both hemispheres in frontal, temporal, parietal and limbic brain areas showed differences strongly biased to the N.G contextual condition. According to the results, the Right IFG with BA 13, Right SFG with BA 6 and the Right Cingulate Gyrus with BA 24 are activated with both positive and negative contrast (see the highlighted results in Table 11). In addition, the left Precentral Gyrus is activated differently in this contrast, which informs different motor response than the other contrasts. Again, there are frontal differences in left and right MFG (up to 46 mm and 44 mm respectively). Results showed that the greatest differences measured occurred towards the most frontal area of the brain, with the greatest frontal differences measuring up to 50 mm in the left SFG and up to 56 mm in the right SFG, having the more frontal activation in the right hemisphere. Overall these differences in the Prefrontal Cortex by the trial before the G condition in analysis are supporting hypothesis H2 and suggest the more frontal activation for the switching from simultaneous Novel and Goal to the Goal which is also concordant with Koechlin's model (2003) of the frontal episodic attention control and with Corbetta's model (2008) lateralising to the right hemisphere.

In table 11 there are also shown the frontal differences in the left and right Anterior Cingulate Cortex (ACC, up to 34 mm and 30 mm respectively), this is consistent with the view that ACC is involved in conflict monitoring (reviewed by van Veen & Carter, 2002) which is the previous context in our analysis.

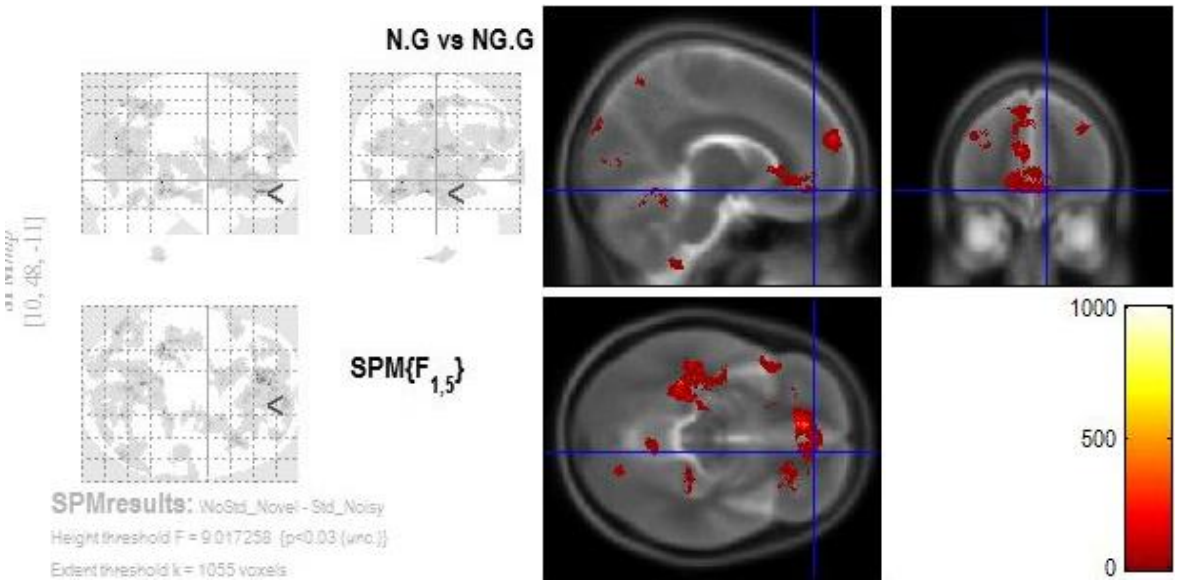


Figure 36 Brain regions for the contrast between sequences N.G and NG.G as conditions. A) Glass brain images pointing to the maximum F value in the Right Precentral Gyrus [10 48 11]. B) Cross sectional images with the blue cross bars point to the maximum F value in the Left Left Medial Frontal Gyrus at MNI voxel [10 48 11].

Table 11

Brain areas and statistical results of the 'distracted' subgroup (n = 6) with p < .03 and 1055 voxels activated for Novel and Goal vs simultaneous Novel and Goal and Goal: N.G vs

Significant brain areas activated Positive difference	Voxels with maximum T value *Statistics*		*Coordinates*			*Brodmann areas*
	F value	*p value*	*x*	*y*	*z*	
Frontal lobes						
1 R InferiorFrontal Gyrus	6.83	< .001	43	18	13	13,45
2 R MedialFrontal Gyrus	13.28	< .001	13	10	44	32,6
3 R MiddleFrontal Gyrus	9.20	< .001	19	-10	60	6
4 R PrecentralGyrus	2.62	.023	11	-17	63	6
5 R Sub Gyral	3.91	.006	18	-6	56	6
6 R SuperiorFrontal Gyrus	6.36	< .001	9	-15	67	6
Parietal lobes						
7 R InferiorParietal Lobule	3.77	.007	46	-28	30	40
8 R PostcentralGyrus	4.03	.005	66	-17	19	40,43
Temporal lobes						
9 R MiddleTemporal Gyrus	3.61	.008	65	-9	-3	21
10 R SuperiorTemporal Gyrus	8.12	< .001	68	-31	14	22,41,42
11 R TransverseTemporal Gyrus	6.38	< .001	49	-20	12	41,42
Occipital lobes						
Limbic lobes						
12 R CingulateGyrus	18.90	< .001	14	7	43	24,32

Significant brain areas activated Negative difference	Voxels with maximum T value *Statistics*		*Coordinates*			*Brodmann areas*
	F value	*p value*	*x*	*y*	*z*	
Frontal lobes						
1 L InferiorFrontal Gyrus	11.34	< .001	-46	19	-7	44,45,47
2 L MedialFrontal Gyrus	24.70	< .001	-5	46	12	10,11,9
3 L MiddleFrontal Gyrus	14.95	< .001	-26	34	-14	11,6
4 L ParacentralLobule	15.62	< .001	-9	-39	51	5
5 L PrecentralGyrus	6.83	< .001	-57	14	6	44
6 L SuperiorFrontal Gyrus	10.92	< .001	-10	50	23	6,8,9
7 R InferiorFrontal Gyrus	11.91	< .001	34	16	-15	13,47
8 R MedialFrontal Gyrus	11.61	< .001	5	44	-12	10,11
9 R ParacentralLobule	10.02	< .001	2	-35	53	5
10 R SuperiorFrontal Gyrus	10.60	< .001	35	56	17	10,6,8
Parietal lobes						
11 L AngularGyrus	11.66	< .001	-46	-70	36	39
12 L Precuneus	31.63	< .001	-5	-49	52	19,31,39,7
13 R AngularGyrus	12.64	< .001	50	-67	31	39
14 R Precuneus	13.69	< .001	4	-54	53	7
15 R SuperiorParietal Lobule	10.07	< .001	16	-63	55	7
Temporal lobes						
16 L AngularGyrus	8.49	< .001	-48	-73	30	39
17 L FusiformGyrus	4.58	.003	-36	-38	-11	37
18 L MiddleTemporal Gyrus	11.43	< .001	-50	-62	22	39
19 L Sub Gyral	7.50	< .001	-39	-11	-10	21
20 L Sub GyralHippocampus	28.63	< .001	-29	-38	-1	
21 L SuperiorTemporal Gyrus	8.99	< .001	-51	-61	21	38,39
22 R Sub GyralHippocampus	6.32	< .001	29	-30	-6	
Occipital lobes						
23 L Cuneus	8.46	< .001	-20	-67	17	18
24 L Precuneus	15.51	< .001	-3	-59	20	23,31
25 R Cuneus	8.20	< .001	21	-81	12	17
Limbic lobes						
26 L AnteriorCingulate	18.01	< .001	-10	34	-10	32
27 L CingulateGyrus	23.99	< .001	-5	22	27	24,32
28 L ParahippocampalGyrus	18.29	< .001	-30	-37	-7	27,28,36,37
29 L PosteriorCingulate	9.81	< .001	-16	-56	7	30
30 R AnteriorCingulate	14.61	< .001	3	30	0	24
31 R CingulateGyrus	2.82	.018	4	-8	34	24
32 R ParahippocampalGyrus	3.88	.006	20	-34	-9	27,30,35,36
33 R ParahippocampalGyrus Hippocamp	5.02	.002	29	-32	-5	

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

Table 11 (continued)

Brain areas and statistical results of the 'distracted' subgroup (n = 6) with p < .03 and 1055 voxels activated for Novel and Goal vs simultaneous Novel and Goal and Goal: N.G vs

Significant brain areas activated Positive difference	Voxels with maximum T value					*Brodmann areas*
	Statistics		*Coordinates*			
	F value	*p value*	*x*	*y*	*z*	
Deep gray (Sub lobar areas)						
13 R Claustrum	5.88	.001	30	4	15	
14 R Insula	17.83	< .001	37	19	10	13
15 R LentiformNucleusMedialGlobus Pal	16.94	< .001	18	-9	1	
16 R LentiformNucleusPutamen	21.39	< .001	22	9	0	
17 R Thalamus	5.73	.001	14	-13	0	
18 R ThalamusVentral PosteriorLateral N	7.18	< .001	21	-21	8	
19 L Anterior LobeCulmen	7.21	< .001	0	-59	-10	
20 R Anterior LobeCerebellarLingual	6.43	< .001	10	-47	-13	
21 R Anterior LobeCulmen	11.05	< .001	6	-57	-10	
22 R Anterior LobeFastigium	3.35	.01	6	-50	-19	
23 R Anterior Lobe	4.25	.004	23	-48	-25	
24 R Posterior LobeCerebellarTonsil	6.42	< .001	27	-58	-33	
25 R Posterior LobeDeclive	15.38	< .001	4	-58	-11	
26 R Posterior LobePyramis	3.69	.007	10	-69	-23	

Significant brain areas activated Negative difference	Voxels with maximum T value					*Brodmann areas*
	Statistics		*Coordinates*			
	F value	*p value*	*x*	*y*	*z*	
Deep gray (Sub lobar areas)						
34 L CaudateCaudate Head	10.82	< .001	-8	10	-4	
35 L LentiformNucleusLateralGlobus Pal	11.40	< .001	-13	6	-6	
36 R CaudateCaudate Tail	2.67	.022	28	-39	7	
37 R Thalamus	14.87	< .001	22	-30	2	
38 R ThalamusPulvinar	9.73	< .001	22	-33	3	
39 L Anterior LobeCulmen	4.93	.002	-13	-33	-11	
40 R Anterior LobeCulmen	6.58	< .001	13	-39	-12	

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

In table 12, the contrast of sequences N.G and Z.G is shown. Both hemispheres in occipital and limbic brain areas showed differences strongly biased to the Z.G contextual condition and both hemispheres showed activation for frontal, temporal and parietal in positive and negative contrasts. According to the results, the Left MedialFrontal Gyrus, Left SFG, Right MedialFrontal Gyrus, Right MFG, Right Precentral Gyrus, Right SFG, Left MiddleTemporal Gyrus and Right STG with different BAs are activated with both positive and negative contrast (see the highlighted results in Table 12). Also, Table 12 showed differences in several frontal regions biased to the N.G condition. Again there are frontal differences in left and right MFG (up to 46 mm and 44 mm respectively). Results showed that the greatest differences measured occurred towards the most frontal area of the brain, with the greatest frontal differences measuring up to 50 mm in the left SFG and up to 56 mm in the right SFG, having more frontal activation in the right hemisphere. Overall these differences in the Prefrontal Cortex by the trial before the G condition in analysis support hypothesis H2 and suggest more frontal activation for the switching from simultaneous Novel and Goal to the Goal which is also concordant with Koechlin's model of the frontal episodic attention control and with Corbetta's model lateralising to the right hemisphere.

In Table 11 there are also differences in the left and right Anterior Cingulate Cortex (ACC). This is consistent with the view of ACC in conflict monitoring (van Veen & Carter, 2002) which is the previous context in our analysis.

Table 12

Brain areas and statistical results of the distracted subgroup (n = 6) with p < .03 and 1055 voxels activated for simultaneous Novel and Goal and Goal vs Zero and Goal: NG.G

Significant brain areas activated Positive difference	Voxels with maximum T					*Brodmann areas*
	Statistics		*Coordinates*			
	T	*p*	*x*	*y*	*z*	
Frontal lobes						
1 **L MedialFrontal Gyrus**	4.46	.003	-5	48	26	10,9
2 **L SuperiorFrontal Gyrus**	7.46	<.001	-6	52	23	10,9
3 **R MedialFrontal Gyrus**	6.49	<.001	7	61	18	10,9
4 **R MiddleFrontal Gyrus**	22.90	<.001	47	23	40	46,8,9
5 **R PrecentralGyrus**	4.93	.002	41	17	37	9
6 **R SuperiorFrontal Gyrus**	5.67	.001	26	60	17	10
Parietal lobes						
7 R AngularGyrus	9.05	<.001	49	-66	30	39,40
8 R Precuneus	17.11	<.001	27	-80	39	19,39,7
9 R SupramarginalGyrus	11.63	<.001	61	-51	34	40
Temporal lobes						
10 L FusiformGyrus	16.30	<.001	-32	-39	-16	20,37
11 **L MiddleTemporal Gyrus**	3.64	.007	-37	-81	18	19
12 L Sub Gyral	9.78	<.001	-43	-11	-10	21
13 L Sub GyralHippocampus	11.00	<.001	-29	-39	0	
14 R CaudateCaudateTail	4.17	.004	34	-34	2	
15 R FusiformGyrus	4.48	.003	44	-64	-14	37
16 R MiddleTemporal Gyrus	10.59	<.001	38	-60	28	19,39
17 R Sub GyralHippocampus	7.29	<.001	28	-35	-2	
18 **R SuperiorTemporal Gyrus**	4.97	.002	56	-63	27	39
Occipital lobes						
19 L FusiformGyrus	9.15	<.001	-27	-67	-9	19
20 L LingualGyrus	8.94	<.001	-19	-63	1	18,19
21 L MiddleOccipital Gyrus	9.05	<.001	-35	-84	10	18,19
22 L SuperiorOccipital Gyrus	2.71	.021	-36	-82	23	19
23 R Cuneus	11.24	<.001	19	-84	36	17,18,19
24 R FusiformGyrus	6.51	<.001	44	-67	-14	19
25 R LingualGyrus	6.55	<.001	16	-84	3	17,18
26 R MiddleOccipital Gyrus	8.13	<.001	38	-83	18	18,19
27 R SuperiorOccipital Gyrus	3.04	.014	33	-80	33	19

Significant brain areas activated Negative difference	Voxels with maximum T					*Brodmann areas*
	Statistics		*Coordinates*			
	T	*p*	*x*	*y*	*z*	
Frontal lobes						
1 L InferiorFrontal Gyrus	8.50	<.001	-34	22	8	13
2 **L MedialFrontal Gyrus**	20.68	<.001	-2	-15	63	32,6
3 L MiddleFrontal Gyrus	9.92	<.001	-25	-10	56	6
4 L ParacentralLobule	7.28	<.001	-13	-32	51	5
5 L PostcentralGyrus	9.79	<.001	-19	-28	57	4
6 L PrecentralGyrus	12.61	<.001	-29	-12	54	4,43,6
7 **L SuperiorFrontal Gyrus**	21.05	<.001	-21	5	63	6
8 R InferiorFrontal Gyrus	7.08	<.001	50	40	-13	47
9 **R MedialFrontal Gyrus**	9.00	<.001	3	-17	56	6
10 **R MiddleFrontal Gyrus**	13.40	<.001	47	41	-13	10,11,47
11 **R PrecentralGyrus**	4.84	.002	36	-28	61	4
12 **R SuperiorFrontal Gyrus**	11.03	<.001	4	6	51	6
Parietal lobes		<.001				
13 L PostcentralGyrus	12.66	<.001	-18	-31	58	3
14 R InferiorParietal Lobule	9.12	<.001	63	-43	23	40
15 R PostcentralGyrus	7.38	<.001	12	-32	67	2,3,40,5
Temporal lobes						
16 **L MiddleTemporal Gyrus**	8.10	<.001	-64	-19	-3	21,22,39
17 L SuperiorTemporal Gyrus	21.09	<.001	-65	-31	14	,22,39,41,42
18 L TransverseTemporal Gyrus	12.15	<.001	-39	-32	11	41
19 **R SuperiorTemporal Gyrus**	20.29	<.001	37	-33	17	22,41,42
20 R TransverseTemporal Gyrus	10.00	<.001	43	-30	11	41
Occipital lobes						

Table 12 (continued)

Brain areas and statistical results of the 'distracted' subgroup (n = 6) with p < .03 and 1055 voxels activated for simultaneous Novel and Goal and Goal vs Zero and Goal: NG.G vs Z.G

Significant brain areas activated Positive difference	Voxels with maximum T value *Statistics*		*Coordinates*			*Brodmann areas*
Limbic lobes						
28 L AnteriorCingulate	5.59	< .001	-10	33	-10	32
29 L LingualGyrus	8.32	< .001	-12	-47	2	
30 L ParahippocampalGyrus	17.29	< .001	-30	-37	-9	30,36,37
31 L PosteriorCingulate	8.35	0.0002	-21	-67	6	30
32 R AnteriorCingulate	8.16	< .001	4	36	-4	24,32
33 R ParahippocampalGyrus	16.37	< .001	22	-33	-1	19,27,28,30
34 R ParahippocampalGyrus Amygdala	4.15	< .001	24	-8	-11	
Deep gray (Sub lobar areas)						
35 L CaudateCaudate Body	3.99	.005	-13	8	21	
36 R CaudateCaudate Body	5.45	.001	14	14	17	
37 R ThalamusPulvinar	10.95	< .001	11	-32	9	
38 R Amygdala	3.67	.007	23	-10	-10	
Additional regions						
39 L Anterior LobeCulmen	7.42	< .001	-33	-60	-24	
40 R Anterior LobeCulmen	9.02	< .001	8	-45	1	
41 R Anterior LobeCulmenof Vermis	8.98	< .001	3	-59	1	
42 L Posterior LobeDeclive	13.74	< .001	-37	-72	-17	
43 L Posterior LobeTuber	9.11	< .001	-42	-65	-23	
44 R Posterior LobeDeclive	14.84	< .001	45	-69	-18	
45 R Posterior LobeTuber	13.98	< .001	40	-72	-24	
46 L MidbrainSubstania Nigra	6.79	< .001	-9	-15	-10	
47 R MidbrainMammillary Body	5.07	.002	4	-10	-8	
48 R MidbrainSubstania Nigra	4.65	.003	7	-14	-9	

Significant brain areas activated Negative difference	Voxels with maximum T value *Statistics*		*Coordinates*			*Brodmann areas*
Limbic lobes						
Deep gray (Sub lobar areas)						
21 L Claustrum	7.10	< .001	-32	-22	9	
22 L Insula	33.52	< .001	-55	-36	19	13
23 L LentiformNucleus	8.63	< .001	-13	-1	5	
24 L LentiformNucleusLateralGlobus Pallidu	11.54	< .001	-13	1	4	
25 L LentiformNucleusPutamen	11.33	< .001	-15	3	3	
26 L Thalamus	7.09	< .001	-13	-17	4	
27 L ThalamusMammillary Body	5.10	.002	-11	-18	4	
28 L ThalamusMedial DorsalNucleus	4.16	.004	-8	-15	6	
29 L ThalamusVentral AnteriorNucleus	4.03	.005	-16	-8	11	
30 L ThalamusVentral LateralNucleus	5.28	.002	-10	-12	3	
31 L ThalamusVentral PosteriorLateral Nucl	8.75	< .001	-18	-19	6	
32 L ThalamusVentral PosteriorMedial Nucl	6.03	< .001	-16	-20	6	
33 R Claustrum	12.62	< .001	32	-13	12	
34 R Insula	27.58	< .001	39	-27	17	13
35 R LentiformNucleusPutamen	10.95	< .001	22	11	6	
36 R Thalamus	38.66	< .001	10	-12	1	
37 R ThalamusPulvinar	8.62	< .001	20	-23	15	
38 R ThalamusVentral LateralNucleus	13.42	< .001	10	-14	3	
Additional regions						
39 L MidbrainSubthalamic Nucleus	4.58	.003	-11	-11	-2	
40 R MidbrainSubthalamic Nucleus	23.56	< .001	12	-10	-1	

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

Table 13 shows the contrast of sequences N.G and Z.G. Both hemispheres in parietal brain areas showed differences strongly biased to the Z.G contextual condition and both hemispheres showed activation for frontal, temporal, occipital and limbic in positive and negative contrasts. According to the results, the Right SuperiorTemporal Gyrus with the BA 22 with both positive and negative contrast (see the highlighted results in Table 13). Further, Table 13 showed frontal differences in two frontal regions biased to the N.G condition. In these contrasts, there are frontal differences in right MFG biased on N.G (up to 37 mm). The other great frontal difference is up to 32 mm in the right IFG. Therefore, the more frontal activation occurs in the left hemisphere. Overall, these differences in the Prefrontal Cortex by the trial before the G condition in analysis support hypothesis H2 and suggest more frontal activation for the switching from Novel to the Goal which is also concordant with Koechlin's model of the frontal context attention control and with Corbetta's model lateralising to the right hemisphere.

Table 13 also shows the differences in the left and right Anterior Cingulate Cortex (ACC). This is consistent with the view of ACC in conflict monitoring (van Veen & Carter, 2002) which is the previous context in our analysis.

Table 13

Brain areas and statistical results of the distracted subgroup (n = 6) with p < .03 and 1055 voxels activated for Novel and Goal stimulus vs Zero and Goal conditions: N.G vs Z.G

Significant brain areas activated Positive difference	Voxels with maximum T					*Brodmann*
	Statistics		*Coordinates*			*areas*
	T	*p*	*x*	*y*	*z*	
Frontal lobes						
1 L PrecentralGyrus	4.11	.005	-35	8	36	9
2 R MedialFrontal Gyrus	3.36	.01	18	37	24	9
Parietal lobes						
Temporal lobes						
3 R CaudateCaudateTail	2.81	.019	33	-39	3	
4 R SuperiorTemporal Gyrus	3.32	.011	44	-20	-5	**22**
Occipital lobes						
5 R FusiformGyrus	6.81	<.001	28	-48	-7	37
6 R ParahippocampalGyrus	7.34	<.001	26	-48	-9	37
Limbic lobes						
7 R AnteriorCingulate	3.26	.011	21	34	24	32
8 R ParahippocampalGyrus	5.41	.001	30	-45	-9	19,37
Deep gray (Sub lobar areas)						
9 R ThalamusPulvinar	6.41	<.001	9	-30	9	

Significant brain areas activated Negative difference	Voxels with maximum T					*Brodmann*
	Statistics		*Coordinates*			*areas*
	T	*p*	*x*	*y*	*z*	
Frontal lobes						
1 R InferiorFrontal Gyrus	3.75	.007	27	32	-7	47
2 R PrecentralGyrus	2.51	.027	48	-11	10	13
Parietal lobes						
3 L Precuneus	12.40	<.001	-12	-44	37	31
4 R AngularGyrus	22.84	<.001	47	-70	37	39
5 R InferiorParietal Lobule	15.41	<.001	47	-67	38	39,40
6 R Precuneus	7.92	<.001	44	-70	41	19,39
7 R SupramarginalGyrus	5.96	<.001	62	-46	30	40
Temporal lobes						
8 L MiddleTemporal Gyrus	8.73	<.001	-60	-29	1	21,22
9 L SuperiorTemporal Gyrus	6.08	<.001	-54	-27	1	21,22,41
10 L TransverseTemporal Gyrus	4.16	.004	-40	-31	11	41
11 R MiddleTemporal Gyrus	4.31	.004	52	-63	29	39
12 R SuperiorTemporal Gyrus	4.63	.003	38	-32	16	13,**22**,41
13 R TransverseTemporal Gyrus	3.34	.01	50	-28	10	41
Occipital lobes						
14 L Cuneus	20.87	<.001	-15	-78	29	18,19
15 L Precuneus	18.92	<.001	-7	-57	27	31
16 R Cuneus	6.21	<.001	14	-89	30	19
Limbic lobes						
17 L CingulateGyrus	13.53	<.001	-5	-58	26	31
18 L PosteriorCingulate	14.32	<.001	-6	-58	24	31
Deep gray (Sub lobar areas)						
19 L LentiformNucleus	3.24	.011	-15	-5	4	
20 L LentiformNucleusLateralGlobus Pallidu	4.01	.005	-15	1	5	
21 L LentiformNucleusMedialGlobus Pallidu	3.18	.012	-12	1	2	
22 L LentiformNucleusPutamen	4.00	.005	-18	1	3	
23 L Thalamus	5.08	.002	-9	-9	1	
24 L ThalamusMammillary Body	3.23	.012	-13	-20	2	
25 L ThalamusMedial DorsalNucleus	4.02	.005	-7	-20	3	
26 L ThalamusVentral AnteriorNucleus	3.08	.014	-16	-8	12	
27 L ThalamusVentral LateralNucleus	6.11	<.001	-10	-10	3	
28 L ThalamusVentral PosteriorLateral Nucl	3.19	.012	-17	-22	1	
29 L ThalamusVentral PosteriorMedial Nucl	3.42	.009	-15	-20	3	
30 R Claustrum	8.56	<.001	30	-15	16	
31 R Insula	5.62	.001	43	-17	5	13
32 R LentiformNucleusLateralGlobus Pallidu	3.45	.009	18	-1	3	
33 R LentiformNucleusPutamen	5.97	<.001	29	-12	13	

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

Table 13 (continued)

Brain areas and statistical results of the distracted subgroup (n = 6) with p < .03 and 1055 voxels activated for Novel and Goal stimulus vs Zero and Goal conditions: N.G vs Z.G

Significant brain areas activated Positive difference	Voxels with maximum T					*Brodmann areas*
	Statistics		*Coordinates*			
	T	*p*	*x*	*y*	*z*	
Deep gray (Sub lobar areas)						
Additional regions						
10 R Anterior LobeCulmen	4.30	.004	7	-42	1	

Significant brain areas activated Negative difference	Voxels with maximum T					*Brodmann areas*
	Statistics		*Coordinates*			
	T	*p*	*x*	*y*	*z*	
Deep gray (Sub lobar areas)						
34 R Thalamus	18.17	< .001	9	-24	1	
35 R ThalamusMammillary Body	3.65	.007	12	-22	1	
36 R ThalamusMedial DorsalNucleus	7.42	< .001	7	-19	3	
37 R ThalamusVentral LateralNucleus	3.29	.011	14	-14	3	
Additional regions						
38 L MidbrainSubstania Nigra	5.21	.002	-14	-21	-6	
39 R MidbrainRed Nucleus	3.36	.01	6	-17	-6	
40 R MidbrainSubstania Nigra	3.14	.013	10	-18	-7	

Anatomical labels and associated T statistical values are listed. t scores from the omnibus analyses of 6 participants for each ROI are presented.

3.4 Discussion

The first results discussed here focus on the 'distracted' 6 participant's analysis which showed more significant brain activations than found for the whole group of 11 participants.

The analysis of these fMRI data (1) explored the effect of prior context across participants supporting H2 but only for 'distracted' participants; (2) explored novel response generators and simultaneous novel and target response generators relative to the standard goal condition supporting H1 but only for 'distracted' participants; and (3) attempted to find a possible explanation for the observed smaller than expected Novel sound ERP amplitudes.

3.4.1 Reaction time results suggest that the novelty effect maybe vary between causing alerting and orienting

The reaction times observed in the orienting subgroup were slower (20 to 70 ms) in the simultaneous novel and target (NG) condition suggesting that the focus of attention can be shifted with the introduction of a novel alongside the target in the mental representation of the auditory scene. In the literature we find this range of reaction times in orienting to alerting stimuli (Fan *et al.*, 2005). According to Fan and colleagues, behavioural reaction time differences in alerting would be around 60 ms, orienting around 31 ms and conflict monitoring around 102 ms.

3.4.2 EEG Results suggest that the noise is coming from sound stimulus presentation

According to Debener's experimental studies at 1.5 T, 3 T and 7 T, the higher the magnetic field of the scanner the higher the electrical noise on the EEG recordings (Mullinger, Debener, Coxon, & Bowtell, 2008). The problem of obtaining several trials for ERP measures using the MRI machine has been reported indirectly. For example, Mulert and

colleagues in the simultaneous EEG and fMRI experiment employed 315 standard trials and 75 goal trials to get reliable ERPs and through the use of air tubes to deliver sounds (Mulert et al., 2005). In the present study, obtaining single trial ERPs proved to be an unrealistic goal for a number of reasons. A significant problem was that the sound stimuli that were being played through electrostatic headphones induced an artifact of similar size to the EEG signals in the first few hundred milliseconds of each trial.

The number of trials for single trial average ERP is 6 for the 'distracted' group and 10 for all the participants, i.e. reduction of noise around 2.45 times in the 'distracted' group and 3.16 times for the all participants. On the other hand, the number of trials for the ERPs in Potter's (2008) preliminary analysis was 5 participants at 50 trials per each, giving a total of 250 trials, i.e. a reduction of noise around 15.8 times.

The quality of the recordings was variable in this first ever simultaneous EEG/fMRI recording in this lab and reliable removal of scanner and cardio ballistic artifacts proved to be highly challenging.

Yan and colleagues simulated EEG artifacts aiming to explore Debener's results in artifacts in EEG signals at 3 T of MRI environment. First, a blood inducing Hall voltage was analysed, and EEG artifacts around 200 uV were observed in the left and right electrodes (F7 and F8) of different amplitudes in the first few trials. Moreover, when slow head movements were simulated, EEG artifacts of several hundred of uV in amplitude were observed (Yan, Mullinger, Geirsdottir, & Bowtell, 2010). Although, we did not considered the possible source of the pulse artefact, our results pointed to artefact of several hundred of uV after using an average template. Therefore, based on the EEG results (section 3.3.2), we suggest

re-formulating the filtering of the EEG data bearing in mind the difference between filtered and non-filtered signals and the source of the pulse artifact studying head movements in the simultaneous EEG and fMRI experiment.

Originally our approach sought to link the analysis of individual items to the general linear model in SPM, using linear modelling under EEGLAB (LIMO in Pernet et al., 2011), in a similar analysis to that carried out by Debener and colleagues (Debener et al., 2006) in which they used elements of the ERP response as predictors of fMRI signals. In the present experiment, the number of trials is 400 and the noise in EEG signal responses without auditory effects over electrodes in some cases is less than 100 trials. Added to the change of the variable artifacts at each trial concordant with the problems reported in other studies (e.g. Yan et al., 2010, Debener et al, 2007) the present number of trials of around 100 is small in order to get enough good trials to use the second technique LIMO (explored in chapter 2) as carried out in the only EEG experiment with both control and schizophrenic patients with 600 trials and more than 500 effective trials for each participant. Further, in order to use the single trial ERP and to analyse the contextual control of attention, more participants would be needed to reduce the noise in the EEG average across-subjects. Therefore it is proposed to expand the experiment to up to 25 participants to reduce the noise 5 times, which is slightly greater than the number of participants in the experiment with controls and schizophrenics as discussed in chapter 2.

3.4.3 fMRI for 'distracted' participants showed left and right brain areas in the attention model (H1).

The graphic in *Figure 37* shows that N vs. G show more right parietal lateralized differences while Z vs. G showed left parietal activations. These results are consistent with Corbetta and

Shulman's model of attention (Corbetta & Shulman, 2002) and with the parietal sources of attention for P3a suggested by Polich (2007). Also NG vs. G has differences spread in several brain areas.

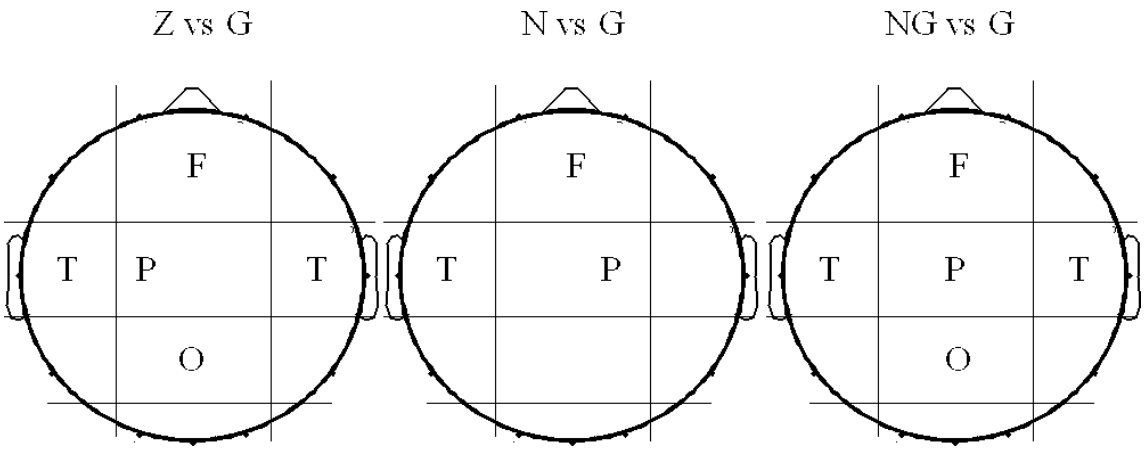


Figure 37 Comparison of the different brain regions for the contrasts Z vs. G, N vs. G and NG vs. G conditions.

The results of this work are discussed in the context of the model of attention, proposed by Corbetta: the areas identified in this model are the Left and Right FEF in Brodmann Area 8, the Left and Right MFG, the Left and Right IFG, the Left and Right IPL, the Left and Right STG, and the Left and IntraParietal Sulcus (L IPs and R IPs) (Corbetta & Shulmann, 2002; Corbetta et al., 2008).

N vs. G contrast, considered in the context of Corbetta's model of reorienting of attention. The results of the did show different activation of the MFG for contrast N vs G and G vs N but they did not show clear differences for the R IPs or close brain areas. Although these results are not clearly consistent with the reorienting of attention *per* Corbetta and colleagues (2008), they support the stimulus driven attention network of Corbetta and Shulman (2002). Brain Areas involved in the orienting response (*i.e.* GD+SD) were visualized when Goal and

Novel only conditions were contrasted and there were found reduced motor activation and enhanced frontal inhibition systems activation.

Moreover, another area related to auditory stimulus processing in Kiehl's results were the left Transverse Temporal Gyri (TTG) which was activated for Goal over Novel stimuli ($p < .001$ FWE) with local probabilities for Goal and Novel of 10 % and 10 %, respectively (Kiehl et al., 2005). To this author's knowledge, there are no articles focussing on Novel stimulus to discuss this TTG area at different local probabilities such as in the present experiment. However, in the two-oddball tasks the TTG appears biased to the infrequent target. For example, Stevens and colleagues found this bias, having 12 standard non-goal stimuli between the infrequent target (Stevens, Skudlarski, Gatenby & Gore, 2000). In our results, the TTG appears more activated in both hemispheres biased to the N condition over the G condition. A possible reason may be the local probability of the N condition 12.5 % vs. the local probability of the G condition of 62.5%. Therefore, the present results added to the literature, suggesting that the auditory cortex is modulated by the local probability.

In the present results, the more dorsal R SFG appeared activated on both contrasts instead of the R FEF and this would change not only the top-down control but also the stimulus-driven network changing the R FEF to the Right SFG. However, this may simply be a consequence of normalisation not working as well due here to the small population of participants.

NG vs. G contrast and the Corbetta model of reorienting of attention

Extending this discussion of the attention model and the auditory task, taking into account that the results are consistent with the activation of the stimulus driven attention network of Corbetta and Shulman (2002). Although, the positive contrast results are not exactly

consistent with the reorienting of attention of Corbetta and colleagues (2008), activation in Brodmann Areas 7, 19 and 39 are possibly consistent with activation of the R IPs. On the other hand, the negative contrast (biased to G condition) showed a different activation in the Brodmann Area 40 and the SPL indicating a weak relationship with the R IPs and the TTG indicating a greater activation of the auditory cortex for the G condition, corroborating Kiehl's results for a Goal condition (Kiehl et. al. 2005). Moreover this negative contrast is consistent with the reorienting of attention of Corbetta and colleagues (2008). These interpretations suggest that the NG condition is possibly evoking a similar pattern to orienting of attention, while the IPs is suppressed, possibly due to an auditory cortical bias for the G condition. This possibly affects R MFG having R Medial Frontal Gyrus instead.

Z vs. G contrast contrast and the Corbetta model of reorienting of attention

Finally, concluding this relation between the attention model and the auditory task, taking into account the results of the positive contrast results, however, are not consistent with the reorienting of attention of Corbetta and colleagues (2008). Although several areas of the right hemisphere were with relatively greater to the Z condition, the FEF and IPL are not clearly activated or deactivated. These interpretations suggest that the Z condition is evoking a similar pattern to control of attention without difference of the Transverse Temporal Gyrus for the Numbers in Z and G condition, *i.e.* the stimulus driven control of attention in the model of Corbetta and Shulman (2002). Response inhibition were supported by frontal areas in the, Goal vs. Zero conditions, therefore this supports the idea of the capacity to inhibite unsuitable actions in this task for this group of participants.

Brain areas of specific interest in the number parity decision task

In the case of the parietal lobes: in the Z vs. G contrast the Right Precuneus were similarly

activated only in this contrast; in the **NG vs. G contrast** the L/R Angular Gyrus, L/R Inferior Parietal Lobule **and Left Superior Parietal Lobule** (SPL) showed different activations only in this contrast for F-value difference; and in the **N vs. G contrast the Left Precuneus showed similar activations only in this contrast** while in the motor cortex the Right Paracentral Lobule showed different activations only in this contrast. Therefore in the NG vs. G contrast IPL and SPL showed different activations. Activation in the Precuneus ($p \leq .0005$ uncorrected) is of interest because Precuneus is associated with reaching activity (Astafiev et al., 2003; Connolly, Goodale, Menon, & Munoz, 2003). Although in the present experiment the hand is not reaching different places, the selected finger (index or middle) is reaching the button for the task, the Goal and Novel stimulus showed an activation similar to the tendency to reach the novel, with different brain activations suppressing the button press in N vs. G more in the right Precuneus and allowing the button press in NG vs. G and Z vs. G in left and right Precuneus. Taking altogether the results for the contrast NG vs. G there is consistent with recent subdural electrodes in humans in the IPS, SPL and Precuneus for reaching a cup from a resting position (Inouchi et al., 2013).

On the temporal lobes: in the Z vs. G contrast the Left Sub Gyral area showed similar activations only in this contrast while in the different contrasts the L/R Transverse Temporal Gyrus (TTG) showed different activations. This is consistent with result of the 750 Hz tone which activated more voxels in the medial area of the TTG whereas the 2000 Hz tone activated more voxels in the lateral TTG (Melendez-Colino et al., 2007). Moreover, the Right Superior Temporal Gyrus (STG) has different activations in the different contrasts, which has been reported to be activated more by speech and frequency modulated tones (Binder et al., 2000); in the NG vs. G contrast the L/R Angular Gyrus, Left Fusiform Gyrus, L/R Sub Gyral Hippocampus and Right Middle Temporal Gyrus showed different activations only in this

contrast.

In the case of the occipital lobes: in the Z vs. G contrast the Right Fusiform Gyrus showed different activations only in this contrast; in the NG vs. G contrast the Right Cuneus/Precuneus Right Lingual Gyrus and Right Superior Occipital Gyrus showed different activations only in this contrast; and in the N vs. G contrast the Left Cuneus/Precuneus showed similar activations only in this contrast. FusiformGyrus activation reduces with repeated presentations, also when the performance of the participant is better (Schacter & Buckner, 1998). In the present results, the L FusiformGyrus is more activated in the Novel than the Z and NG conditions, having clear differences at Goal as an object identification. However, there is no clear difference in the contrast of different conditions N vs G and N.G vs G.G. This supports the view that the orienting response is sensitive to the degree of familiarity with the experiment (Henson, Shallice, & Dollan, 2000)

3.4.4 Prefrontal cortex and motor responses in the preceding trial (H2)

Results showed that the Precentral Gyrus (PrG) motor area was activated differently in Z vs. G, N vs. G and NG vs. G contrasts. Activations were more ventral with relatively greater activations for the N condition (BA 43), and with relatively greater activations in different BAs in the NG vs. G contrast, in the left BA 6 for the NG condition and right BAs 4, 6 and 44 with relatively greater activations for the G condition. Moreover, taking into account the contextual contrasts, activations for Z.G vs. G.G contrast produced larger activation in the Right PrG (BAs 4 and 6) and for the N.G vs. G.G contrast had relatively greater activations for the N.G condition on the Left PrG (BA 4) and Right PrG (BA 4, 44 and 6). Therefore overall all these results different prefrontal control is seen at PrG

Although motor response is usually activated in the contralateral side, in this experiment the right hand was used in the parity decision task whilst some ipsilateral responses in the Left PrG were activated for N.G condition over G.G condition. Considering the change of the fundamental frequencies between N and G conditions, this left ipsilateral result to the right hand of response is consistent with frequency changes greater than 30 Hz observed for harmonic tones (Rinne et al., 2007). Thus, the Novel before a Goal makes more contribution to different motor area activations and similar activations than the NG conditions. Therefore, the 'distracted' participants showed a stronger attention to the task than to the motor control in N vs. G contrast and the motor control switch between N.G and G.G conditions, which is similar to the conflict motor control switch between NG and G conditions. Therefore, the motor response may be used in explaining the prefrontal control in the light of H2. This part of the discussion is expanded in the next part of the discussion which studies context from the point of view of the previous trial.

3.4.5 Prefrontal cortex and context given by the immediately previous trial (H2)

Tables 10 and 11 show that there are more differences in NG.G vs. N.G than in G.G vs. N.G, consisting of more frontal areas and towards to the front as well for NG,G vs. N,G, which is consistent with the different frontal activations in the contextual approach of the hypothesis H2.

More insights derived from the results driven by hypothesis H2 are analysed in Table 14. This shows the comparison of the five contrasts analysed (first column). From Z,G vs. G.G to N.G vs. Z.G contrasts, it looks like the effect of a previous Novel stimulus is to increase the activation of the prefrontal areas. When both contrasts are compared to the N.G vs. G.G contrast, this increased activation of additional prefrontal areas is corroborated, and also the change of motor response results analysed in the previous section (3.4.4) in the activation of

additional prefrontal areas. In Table 14, when the first and third row are compared with the fourth and fifth row, respectively, a similar increase of the number of areas in the prefrontal region is shown. Result suggested, in Table 14, when instead of G is NG part of the increased are because of the recruiting of the brain areas closer to the ACC.

Table 14

Input / Output comparison of the number of Brain areas for the different contextual contrasts

	Previous output	*Current output (Positive T-value)*			*Current output (Negative T-value)*			*Table reported*
Contrasts	*Previous Motor response*	*Number of frontal areas activated*	*Max frontal axis (mm)*		*Number of frontal areas activated*	*Max frontal axis (mm)*		
			Left	*Right*		*Left*	*Right*	
Z.G vs G.G	not vs do	9	-24	28	1	39	-	Table 09
N.G vs Z.G	not vs not	2	8	37	2	-	32	Table 13
N.G vs G.G	not vs do	9	41	37	-	-	-	Table 10
NG.G vs Z.G	do vs not	6	52	61	12	22	41	Table 12
NG.G vs N.G	do vs not	6	-	18	10	50	56	Table 11

ACC activation was shown in both hemispheres (see Tables 11 and 12) related to NG.G (versus N.G and Z.G) and in the left hemisphere (see Table 10) related to N.G (versus G.G). First, this ACC activation is consistent with the view that the ACC facilitates control of attention (van Essen & Carter, 2002). These results showed consistency with conflict monitoring being more frontal and deeper for NG.G vs. N.G contrast, see Left ACC at (-10, 34, -10) mm and the Right ACC at (3, 30, 0) mm in Table 11). Alongside the comparison in the Table 14, these results in frontal areas are not only consistent with the prefrontal control proposed by Koechlin and colleagues (Koechlin et al., 2003), but the R SMG is also consistent with the model of control of attention proposed by Corbetta and colleagues (Corbetta & Shulman, 2002).

3.4.6 fMRI for 'distracted' participants showed left and right brain areas for contextual conditions in the attention model (H1 & H2)

First, the results of the Z.G vs. G.G contrast showed different right parietal activation and no different occipital areas as the signature of this contrast. The results are summarized in the graphic in *Figure 38* and are not completely consistent with the stimulus driven attention network model of Corbetta and Shulman (2002) as shown for the left hemisphere in the dotted rectangle in yellow. Although, the positive contrast results are not exactly consistent with the reorienting of attention of Corbetta and colleagues (2008), the activations in Brodmann Areas 7, 19 and 39 may be related to activity in the R IPs. However, the FEF is not clearly activated. In addition, the negative contrast only showed significant activation of the left Medial Frontal Gyrus without a clear different activation of the control of attention for the G.G condition. Of course, this can be explained because the current trial (G) has mostly the same properties of the frequently previous trial type (G). These interpretations suggest that the Z.G is evoking an interaction of the stimulus and goal driven network differently to the pattern orienting of attention, while the IPs is suggested to be related to BAs 7, 19 and 39 (see dotted rectangle in green).

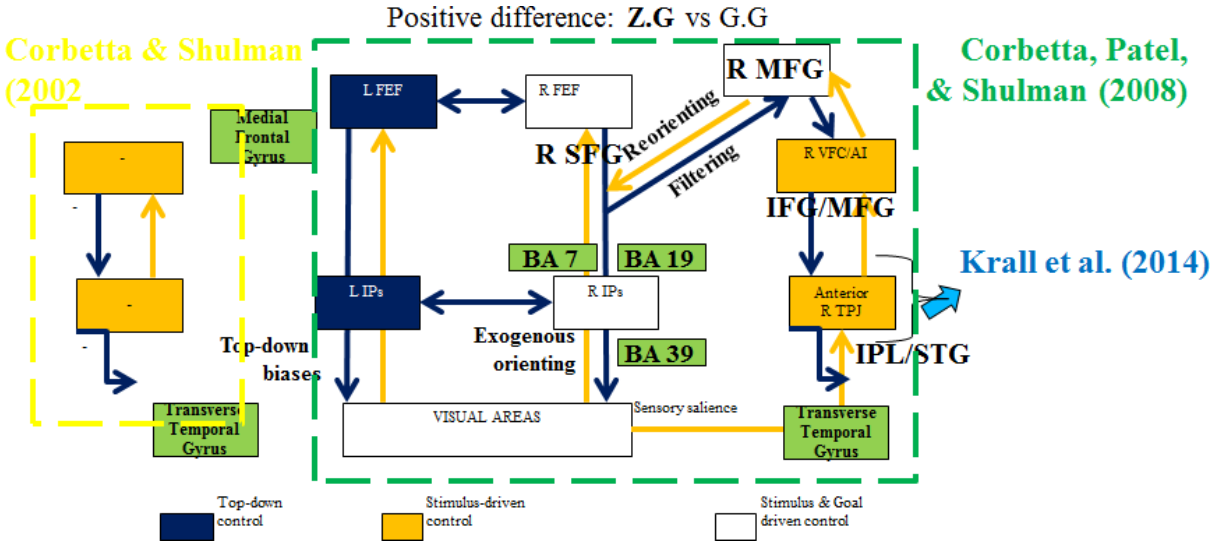


Figure 38 Comparison of the positive and negative difference of the brain areas for the contrast Z.G vs. G.G, showing an interaction between Filtering and Reorienting mode of attention.

Second, when the N.G and G.G contextual conditions are more involved in a different frontal control of attention. The results of the N.G vs. G.G contrast showed different left and right parietal activation and no differences in occipital areas as the signature of this contrast. The results are summarized in the graphic in *Figure 39*. The results support right and left (see dotted rectangle in yellow) hemispheres in the the stimulus driven attention network of Corbetta and Shulman (2002) suggesting the control of attention in the N.G sequence. Although, the positive contrast results are not exactly consistent with the reorienting of attention of Corbetta and colleagues (2008), but the Brodmann Areas 7, 40 and 39 may be enclosing the activity in the R IPs. Further, the negative contrast only did not show significant activation of the cortex; again, this can be explained because the current trial (G) has mostly the same properties of the previous trial (G). These interpretations suggest that the N.G is evoking an interaction of the stimulus and goal driven network similar to the pattern orienting of attention (see dotted rectangle in green).

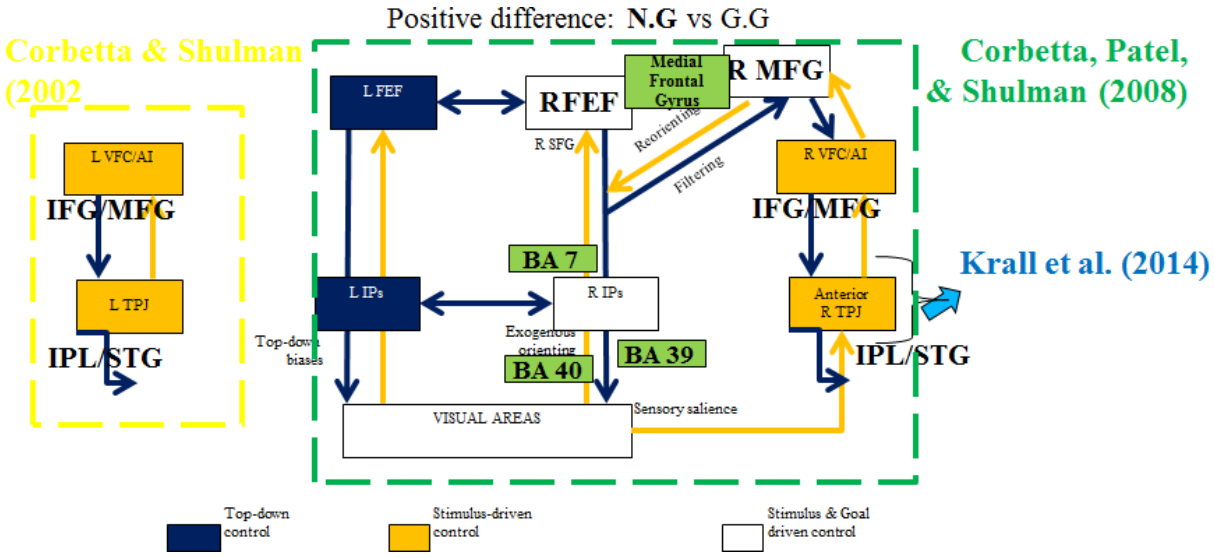


Figure 39 Positive differences of the brain regions for the contrast N.G vs. G.G, showing an interaction between Filtering and Reorienting mode of attention. Several attention areas on the Right hemisphere were with relatively greater activations to the NG condition.

3.4.7 fMRI and ERP comparison and the Anterior Cingulate Cortex

Comparing fMRI and ERP results in the 'distracted' subgroup: (a) The Anterior Cingulate Cortex (ACC) is not activated differently between Z and G conditions (Table 6) and the ERP deflection around 200 ms, biased for Z condition negatively to the left frontal electrode F7 and positively to the right frontal electrode F8 in Figure 26; (b) Right ACC is activated differently between NG and G conditions (Table 8) being more frontal for NG condition in the right ACC (BA 32) and more posterior for the G condition (BA 32) and the negative ERP deflection around 200 ms in the right electrode F8 (in Figure 26) and stronger Left ACC is activated differently between NG and G conditions (Table 8) being with relatively greater for the NG condition in the left ACC (BA 32) and the negative ERP deflection around 200 ms is stronger to the left frontal electrode F7 (in Figure 26); (c) difference between N and G conditions (Table 7) and no clear difference around the ERP at 200 ms (F7 and F8 in Figure 26). These results suggest that ACC is linked to N200 for NG condition in both hemispheres. On the other hand, in the N vs. G contrast positive and negative activation differences in ACC were observed and no clear ERP different deflections around 200 ms, namely MisMatch Negativity. This analysis is consistent with the view of N200 and ACC in conflict monitoring studies (van Veen & Carter, 2002). However, but, because of MMN, it is not clear about the Novel effect.

Moreover, ACC activation was shown to be different across the other contextual contrasts (Z.G vs. G.G, N.G vs. G.G, N.G vs. NG.G, NG.G vs. Z.G and N.G vs. Z.G) and the relatively greater activation was shown not only for novel but also for Zero condition. Therefore, ACC relative activations werte sensible to contextual changes depending on Goal (G), Non-Goal (Z and N) and Novel (N and NG) signal.

In the 'distracted' participants, the contrast between NG.G and N.G was evaluated for the

ACC. Results shown relatively greater activation for the N.G condition in the Left (BA 32) and Right (BA 24) ACC. This suggests that ACC produces different activations depending of the previous context for stimulus-driven network and the conflict monitoring effect. When the contrast between NG.G and N.G conditions in 'all the participants' was evaluated, there were no significant differences in ACC activation and this suggests that ACC in the alerting state does not produce different activations for the different Novel trials presented before the current Goal trial. These differences between the 'distracted' and the 'all participants' would explain the difference of the analysis of the ERP at N200 in Potter's (2008) study and ACC in fMRI in the present analysis of the 'distracted' subgroup.

Another possible comparison would be a further eye field activation in fMRI and beta waves in EEG such as was found for higher arousal levels (Matsuda et. al. 2002). The present analysis may accomodate the role of the FEF in attention when the Corbetta's model of attention is considered. Therefore, a further limitation in the present analysis is that this was the third task in the participants and possibly the results for FEF in the 'distracted' participants added to the inhibition of return for Z vs G contrast were related with the arousal level to keep the answer to the task in the auditory attention task.

These consistencies make it of interest to explore the EEG results in more detail and combine with the fMRI analysis to seek for the explanation of these partial consistencies.

3.4.8 fMRI Results suggest STG role in responding to target stimuli

Based on previous findings in the Amygdala and anterior Superior Temporal Gyrus (STG) of the removal or damage in these regions (Johnson, 1988, 1989; Polich & Squire, 1993), Kiehl and colleagues suggested the "adaptive reflexive processing" of some brain areas when they are required. This is, the activation of some brain areas that are not necessarily required in order to succed in the task. They have interpreted this suggestion specifically because the

Amygdala and anterior STG do not distort the ability of participants to detect target stimuli (Kiehl et. al. 2005). Our results showed activation of the right STG in Z vs. G and N vs. G contrasts, but are in the same contrasts for the left STG. With regard to the difference in the left STG activations, when basic conditions are contrasted gave only NG vs G and N vs G. This supports the suggested hypothesis of the "adaptive reflexive processing" of Kiehl's paper (2005) for Novel signals in the left STG.

Moreover, by using the contrasts, taking into account the immediately previous context, the Right STG is activated differently in all cases of contrast tested. But the Left STG is activated differently in most cases (Z.G vs. G.G, NG.G vs. G.G, and N.G vs. G.G) except N.G vs. Z.G and NG.G vs. Z.G contrasts. These different results show that there are no activation differences when compared to NG or N conditions with Z condition followed later by the G condition. This may show that the "adaptive reflexive processing" for this area showed that the NG or N is taking on a different role at recognizing Novel stimuli independently of the Goal or Non-Goal condition. This may be an extension of previous experiments because both local probabilities are different (G at local probability of 62.5 %) and the Goal is mixed with new stimuli (NG local probability of 12.5 %).

On the other hand, the number subtraction does not evoke the activation of the STG whereas number addition evokes its activation (Hamid, Yusoff, Mukari & Mohamad, 2011). According to the present results STG is activated in the contextual control of attention and that would mean that the subtraction on Hamid's experiment may be explained partially as a consequence of the previous context.

Overall, the STG as a part of the TPJ would match the reflexive adaptive processing of Kiehl (2005) and number addition of Hamid (2011) into the framework of a plasticity in the

different routes of brain processing activity in the SDN and GDN for control of attention of Corbetta & Shulman (2002)

3.4.9 Subcortical activations.

As a result of the auditory experiment, the TTG was considered in the fMRI analysis. This region possibly extends the visual reorienting model of Corbetta and colleagues to the auditory modality, but more analysis should be done to assure that this model may be extended to other modalities, for example an importante extension may be to model the subcortical areas inside the model. Therefore, having the advantage that the subcortical regions were compared, according to the literature, the Thalamus pulvinar is believed to channel the goal-driven network (Shipp, 2004). Wróbel and colleagues found a greater amplitude in the Thalamuspulvinar in the beta frequency for cats in visual discrimination than in auditory cues (Wróbel, Ghazaryan, Bekisz, Bogdan & Kamiński, 2007). The pulvinar – FEF connection with diffusion tensor imaging has also been proven (Leh, Chakravarty & Ptito, 2008), and a recent study suggested that the oscillatory activity of the Thalamus pulvinar may influence cortical processing in the visual cortex (Saalman & Kastner, 2011). Therefore an analysis can be carried out by the present experiment with regard to auditory modality.

In the present results, the thalamus pulvinar showed significant differences in the auditory number parity decision task. The Thalamuspulvinar at the Z vs G contrast showed activations that were relatively greater to G (no bias to FEF and Z.G vs G.G biased to G.G), N vs G contrast biased to G (no bias to FEF) and NG vs G contrast biased to NG with a bias to FEF in the fMRI analysis. Also, the Thalamus Pulvinar did not show significant differences in the N.G vs G.G contrast, *i.e.* it is not supporting a funnel activation in the Novel previous context. However, along FEF, the Thalamuspulvinar is biased to NG.G when compared with

N.G condition and biased to NG.G as well when compared to Z.G condition.

Therefore, these results, although they do not provide evidence of different prior contextual effects of Goal and Novel trials, do support the idea that the right thalamus pulvinar has a role in the regulation of Novel signals in Goal and Non-Goal tasks in auditory tasks. This is the mixture of Novel and Goal, which may be influencing the Novel in the top-down mechanism for both the simultaneous NG event and the sequence of the stimulus given by the context. In other words, this is reorienting of attention.

4 DEVELOPMENT OF A PARAMETRIC EXPERIMENT DESIGN AND SIMULATION OF A TRAIN OF STIMULI IN AN AUDITORY ATTENTION TASK

In the first study (Chapter 2), event-related potential (ERP) evidence was found that suggested a dissociation of stimulus-driven (SDN) and goal-driven networks (GDN). However, the single trial analysis with trial properties of the wide range of 'novel' stimuli used in this number parity decision task revealed a difference in spatial lateralisation as a consequence of the type of stimulus used. Moreover, evidence was found that schizophrenics and controls responded differently to these different classes of stimuli. Therefore, further work may give further insight into the effect of stimulus properties on the attention reorienting system. On the other hand, in the second study (Chapter 3), we have found evidence of the importance of stimulus context in the control of the attention reorienting system, which showed different activations in the prefrontal cortex dependent on the immediately previous informational content. Both studies suggest that a new experimental design should be developed that controls stimulus properties and prior information context more systematically to make a better study of the reorienting of attention. One important improvement in the paradigm would be to introduce a longer interval between goal stimuli and the preceding alerting cue in order to allow better visualisation of the orienting response on trials that include preceding distractor stimuli.

A pilot experiment was therefore carried out to determine whether to use white noise or environmental noise as distractors preceding the goal stimulus and how stimulus properties and/or context are influencing auditory orienting of attention. The experiment also included a condition with scanner background noise (SBN) to determine the effect of scanner noise on the orienting response. A stimulus sequence simulation was then run to assist in the design of

the last experiment.

On the basis of the literature reviewed here and the results of the four condition task in controls and schizophrenic patients, it was hypothesized:

H1: The ERP deflections: N1, mismatch negativity (MMN), P300 and re-orienting negativity (RON) will be affected by the scanner background noise, e.g. as Mulert and colleagues (2004) reported N1 measures outside and inside the scanner were different, but they did not address the scanner noise as background (SBN) in the experiment.

H2: Mismatch negativity (MMN), P300 and re-orienting negativity (RON) will be different for the NG condition with P300 being right lateralized when the Environmental Noise is the Novel stimulus compare to the white noise stimuli also employed in Experiment 1 (Chapter 2). The Environmental Noises which have more semantic content will produce more widespread P300 activation and more sound property correlations.

H3: A right lateralized P300 will be activated when White Noise is the Novel stimulus (as described in Experiment 1 (Chapter 2)) but this will not necessarily be followed by the re-orienting negativity (RON) because although the stimulus may cause an enhanced alerting response, this will not lead to a significant orienting response. This will be evident in the form a less widespread P300 activation and reduce correlations between P300 amplitude and electrodes involved in P300 and White Noise sound properties.

H4: Based on previous findings for the Novel cue, P300 will be different in the trial following the NG condition, being possibly left lateralized due to the upcoming TG condition. Therefore, the NG.TG condition should be left lateralized, as ebserved in

Experiment 1 (Chapter 2) in the range of time of 200 to 350 ms for CTOA = 300 ms.

4.1 Pilot experiment to test effects of stimulus type and scanner background noise on attention orienting response

The experiment was conducted on one female participant. The experimental task was an auditory number parity decision task with only two conditions: tone and goal (TG) and novel and goal (NG) (**Figure 40**).

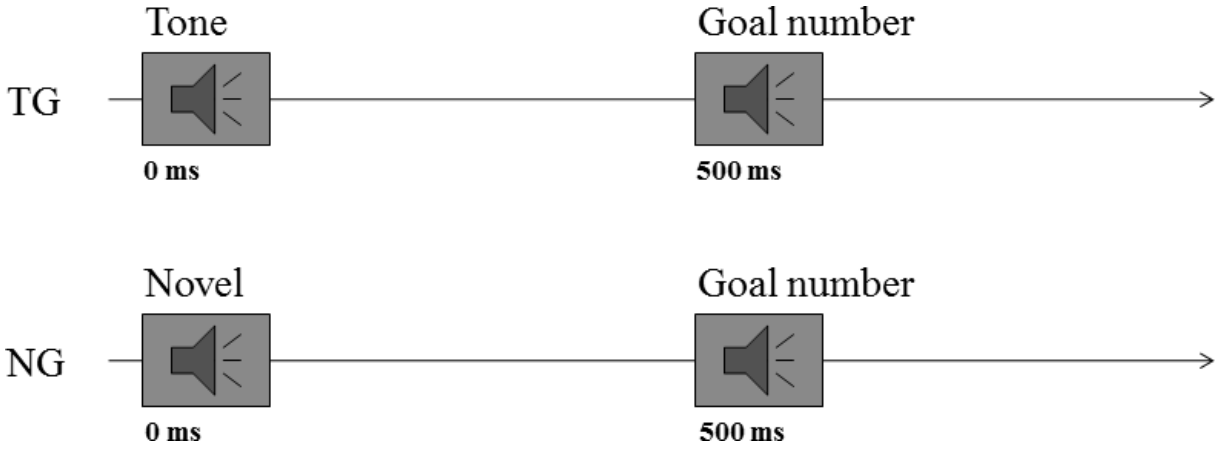


Figure 40 Timing of sounds used per each one of the two different conditions. Note that the time between the either the Tone or the Novel (S1) and the Goal stimulus (S2) is 500 ms. Novel in blocks 1 and 3 is environmental noise and in blocks 2 and 4 is white noise.

These conditions were created to allow analysis of the current TG trial factoring in the previous NG (*i.e.* NG.TG condition in **Figure 40**) or TG condition (*i.e.* TG.TG condition in **Figure 40**). The time between S1 (tone or novel) and S2 (goal) was 500 ms. Eye movements were removed with independent component analysis using EEGLAB routines. Using standard functions in Matlab and Linear Modelling for EEG data (LIMO), two sample t-test differences between conditions for each block was conducted and *t*–test values were plotted without cluster correction. Finally, statistics were run using LIMO for the two conditions (TG and NG) in each block, rendering 4 regressors shown in Figure 41 (2, 5, 8 and 11 for NG)

and for the context dependent analysis sorting on the basis of the previous trial in each block for the condition TG resulting in TG followed by TG (TG.TG see 1, 4, 7 and 10 in Figure 41) and NG followed by TG (NG.TG see 3, 6, 9 and 12 in Figure 41), rendering 12 regressors shown in Figure 41.

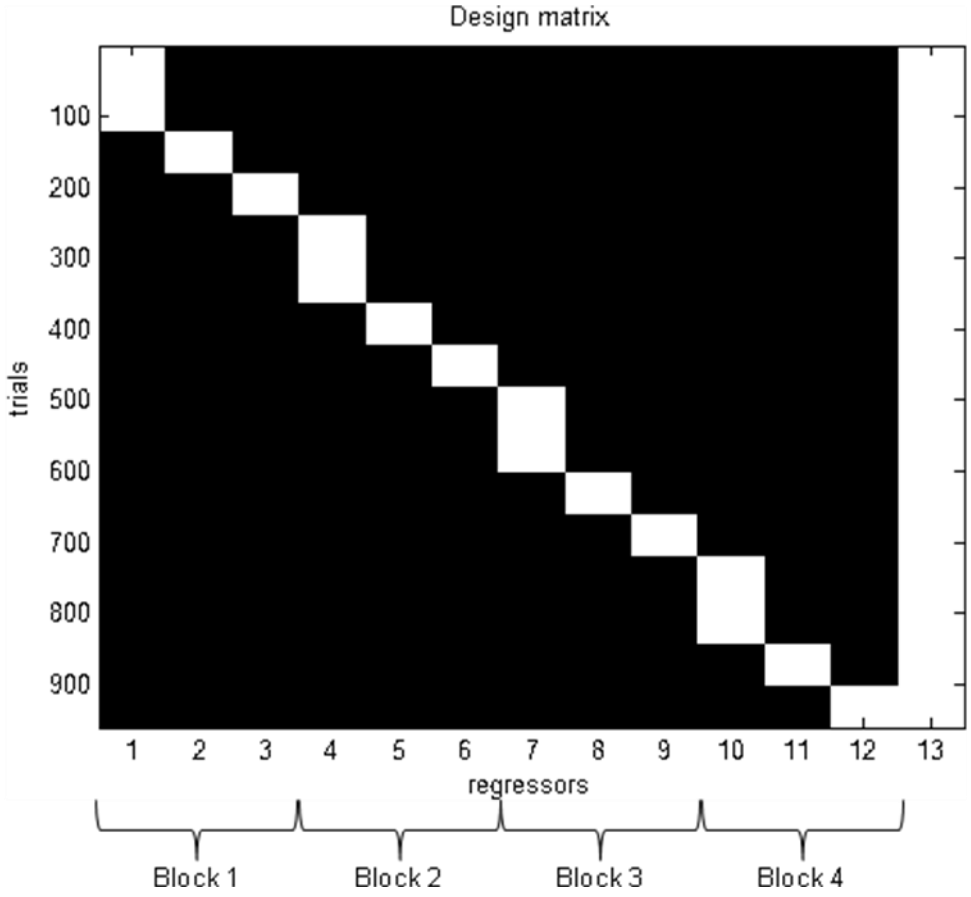


Figure 41 Design matrix for context-dependent categorical analysis. Three regressors were used for each block, resulting in the conditions TG.TG (1, 4, 7 and 10), NG (2, 5, 8 and 11) and NG.TG (3, 6, 9 and 12).

Figure 42 shows the ERP results for all trials in condition TG followed by TG (TG.TG in black lines), NG (or TG.NG in red lines) and NG followed by TG (NG.TG in green lines). The results of ERP difference show for S1 a similar negative deflection around 200 ms and positive deflection after 300 ms, and no clear differences for S2. Also, at the same scale, the

contextual condition NG.TG is not clearly different from TG.TG but it is analysed in detail in the following analysis.

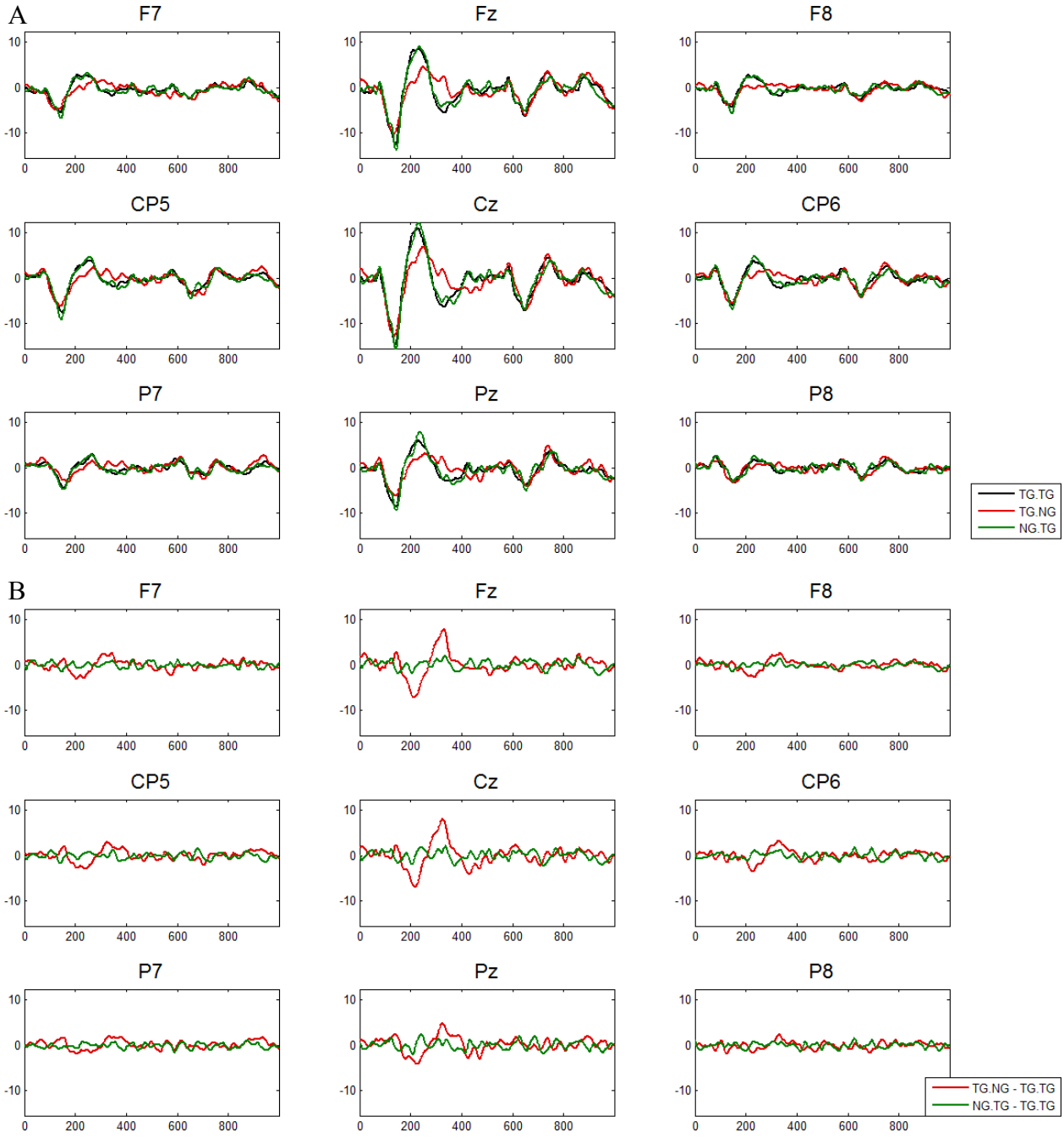


Figure 42 A) ERPs collapsed across all blocks for TG.TG (black), TG.NG (solid red) and TN.TG (solid green) conditions and B) TG.TG subtraction with each one of the last two ERPs, TG.NG (red) and NG.TG (green) at frontal, central and parietal scalp sites. Note that, when all the blocks are considered, although TG.NG – TG.TG shows P300 difference in Fz

and Cz, NG.TG – TG.TG does not show a clear difference across channels.

4.1.1 Linear modelling estimation

A linear estimation with the four conditions as regressors was run. Estimation was significant ($p < .05$) but small ($R2 < .15$) in the first 500 ms for all trials. R2 values showed greatest linear estimation, being greatest from 216 ms, 324 ms, 122 ms, 184 ms, 94 ms and 352 ms with the distributions illustrated on the right Figure 43 parts E, F, C, D, B and G respectively.

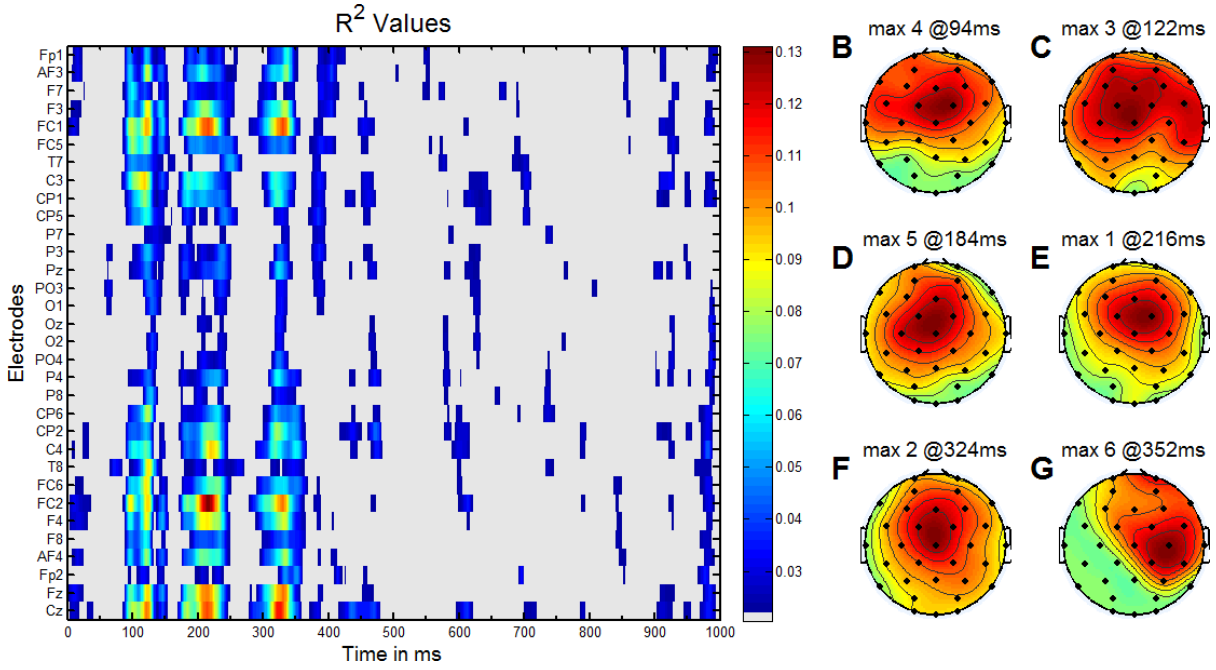


Figure 43 R2 for the linear modelling applied in the EEG data. A. Shows Times x Electrode with amplitude of R2 in colour. B – G show topographical plot of R2 at six local maxima. Max 1 to 6 refers to the rank order of effect magnitude, Max 1 being the largest effect. Note that in all the blocks the explanation of the variance is stronger in the first 500 ms.

Across all the blocks, the ERP deflections for the NG trials are smaller than TG around 70 ms, 144 ms, 182 ms (smallest), 586 ms, 694 ms and 792 ms (Figure 44.B-G). Note that the MMN around 182 ms is evoked in most of the channels (Figure 42B). Over all the blocks,

NG ERP deflections are greater than TG at latencies of around 90 ms, 118 ms (greatest), 318 ms, 630 ms, 920 ms and 982 ms (Figure 45.B-G). Note that the P1 effect around 118 ms is evoked in most of the channels. In addition, although the P300 around 318 ms is right lateralized, the magnitude of the effect is relatively small (sixth peak in Figure 45.D).

Comparing TG and NG, clear significant differences (p = .05) in the mismatch negativity (MMN), P300 and re-orienting negativity (RON) waves were found in the fronto-central channels for the t-test comparison between TG and NG, as shown in the representative electrode Cz in Figure 46. Therefore, the hypothesis H1 is supported for this analysis, but to be completely supported it should appear significant in all the blocks, this is with either environmental and white noise and without or with SBN. This average result is concondant with the view of MMN, P3 and RON in involuntary attention proposed by Yago and colleagues (Yago, Corral, & Escera, 2001). On the other hand, for S2 a negative peak appeared around 694 ms (MMN for S2 in TG condition, second strong peak in Figure 44.F) and a double peak around 920 ms and 984 ms (in S2 for NG condition, third and fourth peaks in Figure 45.F-G).

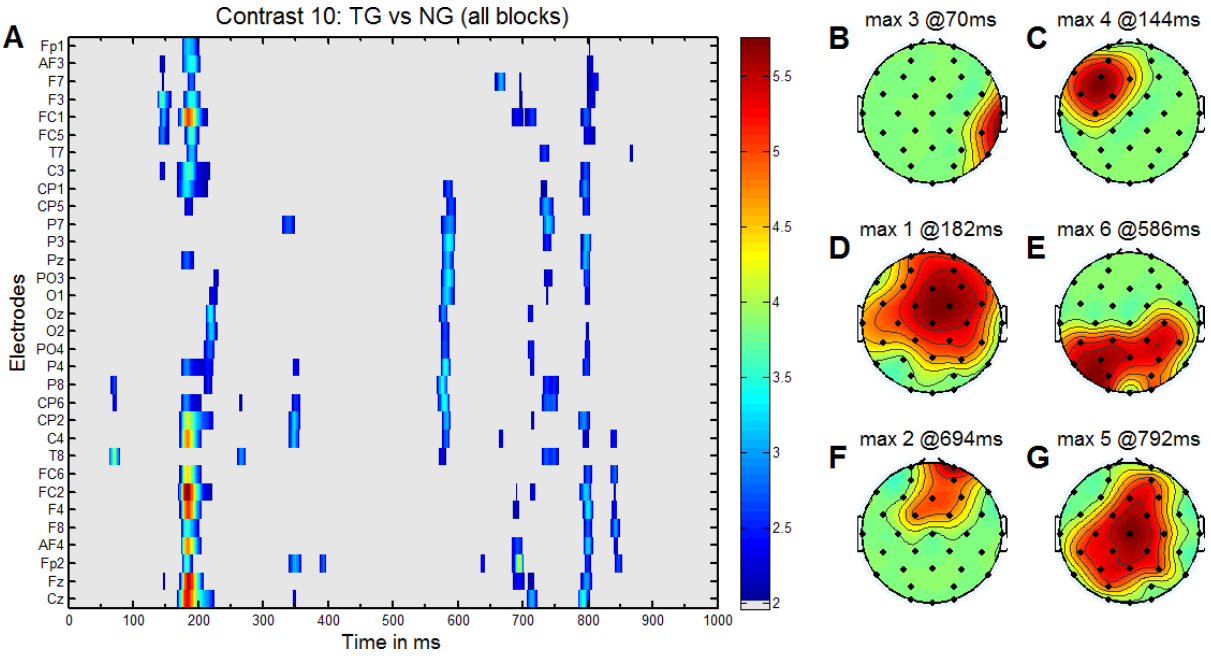


Figure 44 Contrast TG (all blocks) vs. NG (all blocks). Left: Time vs. Electrodes, colour measures amplitude of T values. Right plots: Topographical plot showing local maxima T values. Max 1 to 6 refers to the rank order of effect magnitude, Max 1 being the largest effect.

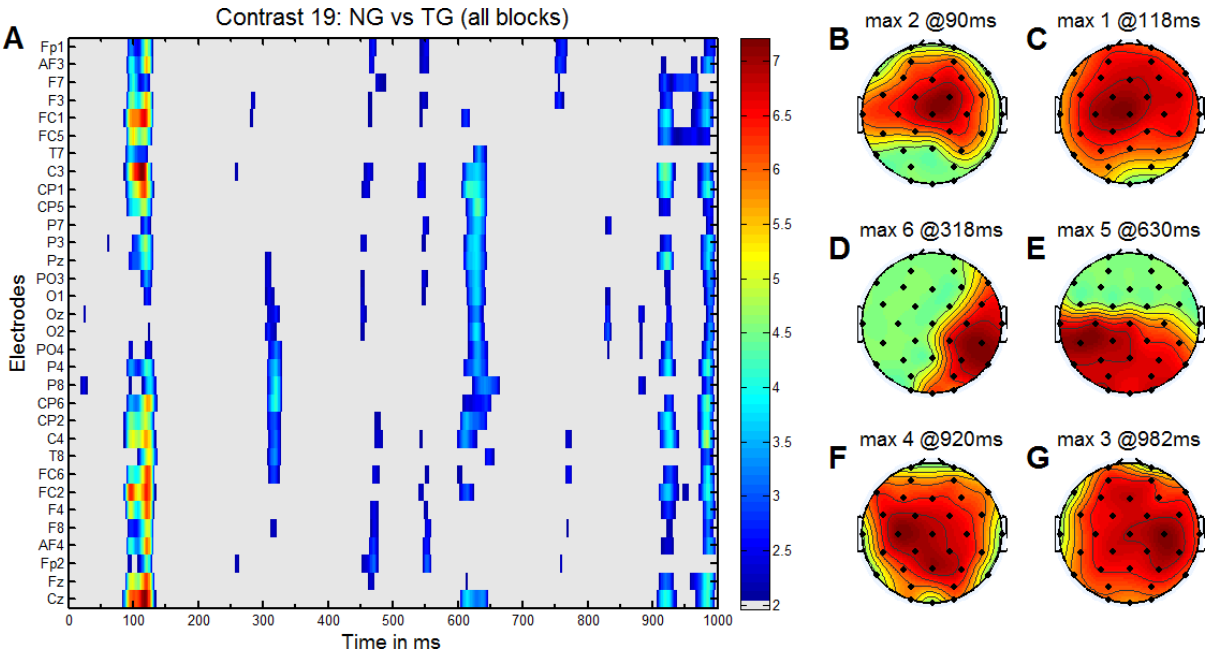


Figure 45 Contrast NG (all blocks) vs. TG (all blocks). Left: Time vs. Electrodes, colour measures amplitude of T values. Right plots: Topographical plot showing local maxima T values.

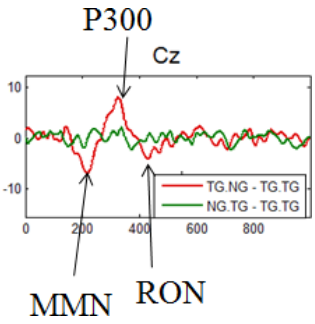


Figure 46 Representative ERP measure (at Cz electrode) indicating the MMN P3 and RON.

4.1.2 Block 1: Environmental noise only

ERP results for trials in block 1, with both differences between conditions NG.TG – TG.TG, and TG-NG shows the biggest difference around 300 ms, consisting of a negative deflection at 200 ms and another negative deflection after 400 ms. Bearing in mind these differences and that R2 is significant with linear estimations, we can analyse the linear estimation.

Significant t-values between conditions in the first 1000 ms were found ($p < .05$) in linear estimation with conditions as regressors in block 1 which considers environmental noise in S1. Topographical plots show greatest F-values for TG from 216 ms, 250 ms, 448 ms, 188 ms, 476 ms and 810 ms (Figure 47 C, D, E, B, F and G respectively) and greatest values for NG from 330 ms, 358 ms, 402 ms, 302 ms, 592 ms and 904 ms (Figure 48 C, D, E, B, F and G respectively). Therefore, it appears that there are significant differences in MMN from 188 up to 250 ms with a maximum at 216 ms (Figure 47 C), a fronto-central negative deflection around 448 ms up to 476 ms is also evident which is most likely the RON wave (Figure 47 E and F) and a P300 peak (Figure 48 G) at 330 ms spreading to the right by 358 ms for NG (Figure 47 C and D). This P300 is the strongest effect in this block, while it was the sixth largest effect in the overall analysis (Figure 45 G). These results for MMN, P300 and RON deflections are consistent with orienting of attention when S1 is an environmental noise. These deflections support partially the hypothesis H1. Moreover, the right lateralized positive

activation for NG condition at 358 ms (Figure 48 D) supports hypothesis H2.

There also appeared a significantly greater value for NG and TG in the second stimulus at 592 ms and 810 ms, respectively, and the sixth greatest value for NG at 904 ms. These results indicate that when the novel appears in S1, S2 would show a greater activation around P100 (592 ms) and a small P3a (904 ms).

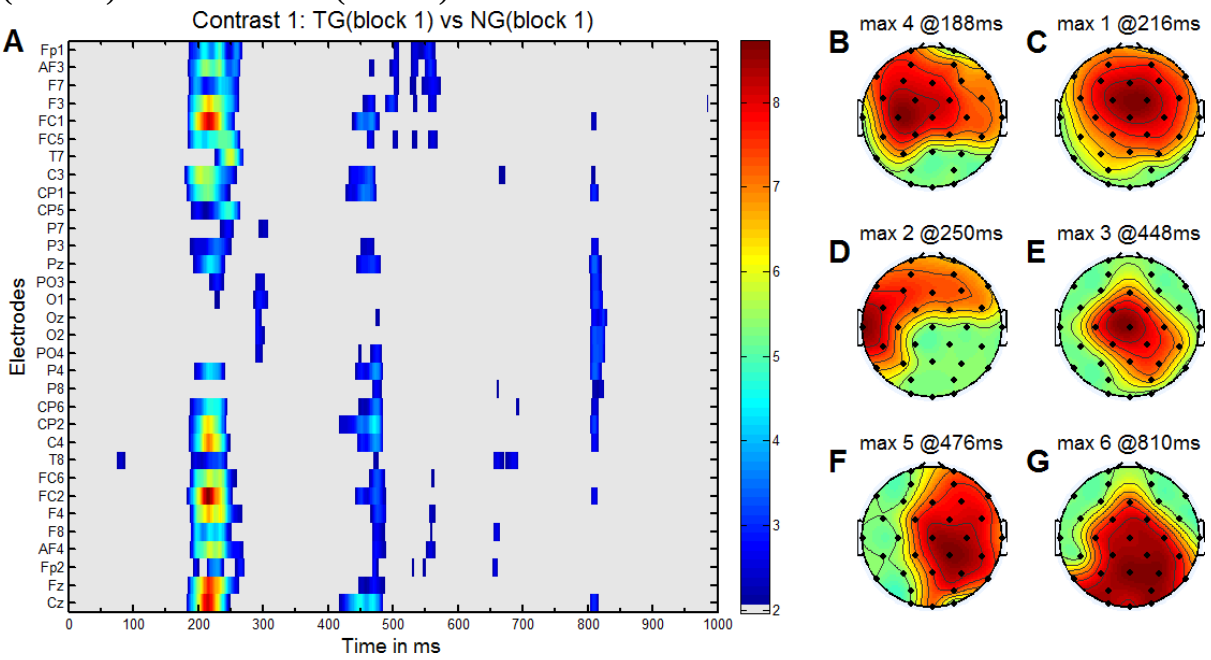


Figure 47 Contrast TG (block 1) vs. NG (block 1). Left: Time vs. Electrodes, colour measures t value. Top right: Topographical plot of t-test value maxima. NG is smaller than TG around 188 ms (B), 216 ms (C), 250 ms (D), 448 ms (E), 476 ms (F) and 810 ms (G). Note that, the MMN is stronger for the Novel in the NG condition around 188 ms in several of the channels.

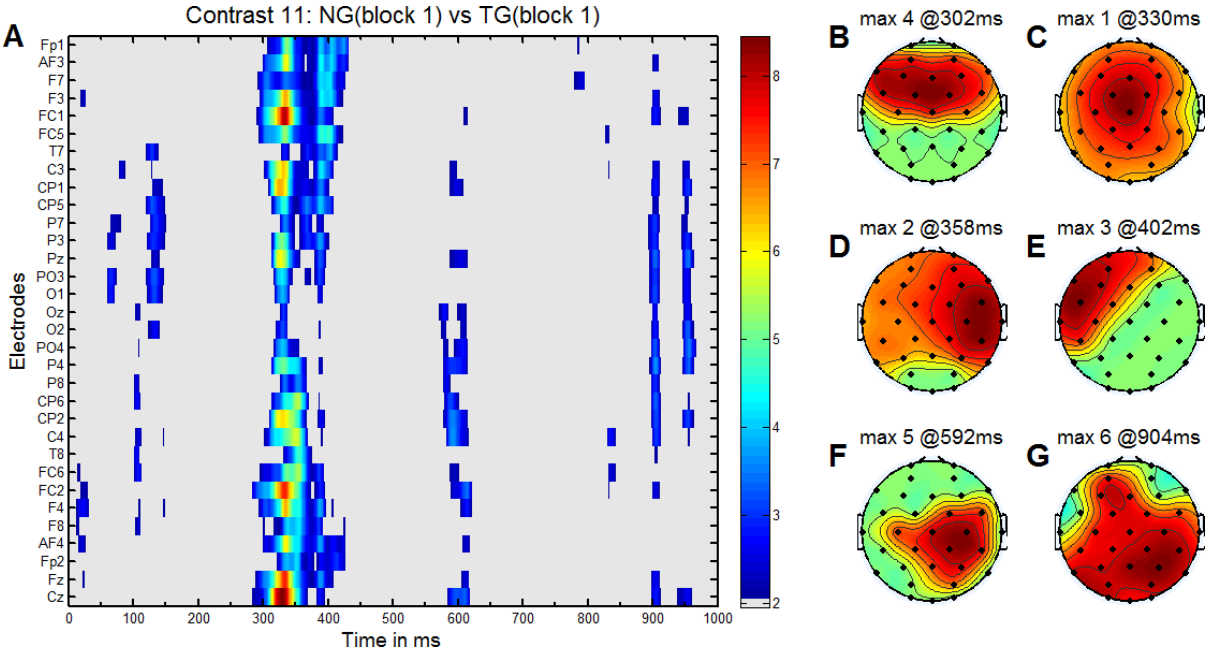


Figure 48 Contrast NG (block 1) vs. TG (block 1). Left: Time vs. Electrodes, colour measures t value amplitude. Right plots: Topographical plot showing local maxima T values. Having the first block, NG is greater than TG around 302 ms (B), 330 ms (C), 356 ms (D), 402 ms (E), 592 ms (F) and 904 ms (G). Note that the P300 is strongly changing between 302 ms and 358 ms and is evoked in most of the channels. Also, P100 is stronger for the Goal in NG condition around 592 ms is central and right parietal lateralized on the scalp.

Prior trial context-dependent effects were explored when the previous event was NG or TG. The P300 showed a significant left fronto-temporal scalp difference in peaks at 378 ms greater for TG.TG (Figure 49 D) and 346 ms greater for NG.TG (Figure 50 D). For this participant, this result indicates that NG activates the alerting system for the following TG: (1) producing shorter ERP latencies, *i.e.* $t_{(P300,\ NG.TG)}$ = 346 ms < 378 ms = $t_{(P300,\ TG.TG)}$; and (2) producing a larger ERP deflection around 436 ms. This last result would suggest a RON for TG.TG, therefore this result does not converge with the view of a RON wave given by an unexpected stimulus and this suggests that a different process is happening. This process can

be related by a bigger P100 (148 ms, Figure 49 C) for TG.TG condition that produces faster ERP deflections. Therefore, although the P300 appeared left lateralized in the NG.TG condition, hypothesis H4 is not clearly supported.

Results for S2 in this contrast shows a more significant effect ($p < .05$) at right fronto-central-parietal electrodes for TG.TG than for NG.TG at 720 ms, and bearing in mind the wideness around 720 ms shown in Figure 49 F, and bigger for in parietal-occipital on the scalp for NG.TG at 760 ms shown in Figure 50 G. These results would possibly reflect a complementary influence of context-effect of the environmental noise in the processing of the goal stimulus.

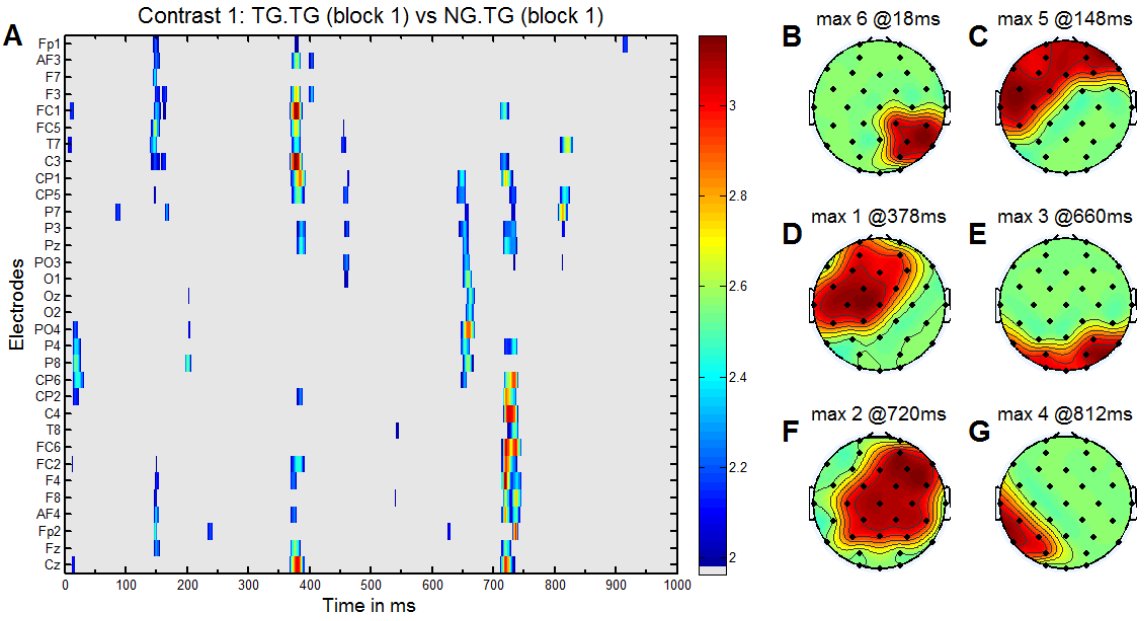


Figure 49 Contrast TG.TG (block 1) vs. NG.TG (block 1). Left: Time x Electrodes, colour measures T value amplitude. Right plots: Topographical plot showing local maxima T values. In the first block, NG.TG is smaller than TG.TG around 18 ms (B), 148 ms (C), 378 ms (D), 660 ms (E), 720 ms (F) and 812 ms (G). Note that the MMN for NG.TG around 188 ms is evoked in several of the channels. Note that the P300 is stronger for TG.TG condition around 378 ms evoked at left fronto-parietal channels. Also, P160 and P220 for Goal in TG.TG

condition around 592 ms are central and right parietal lateralized on the scalp.

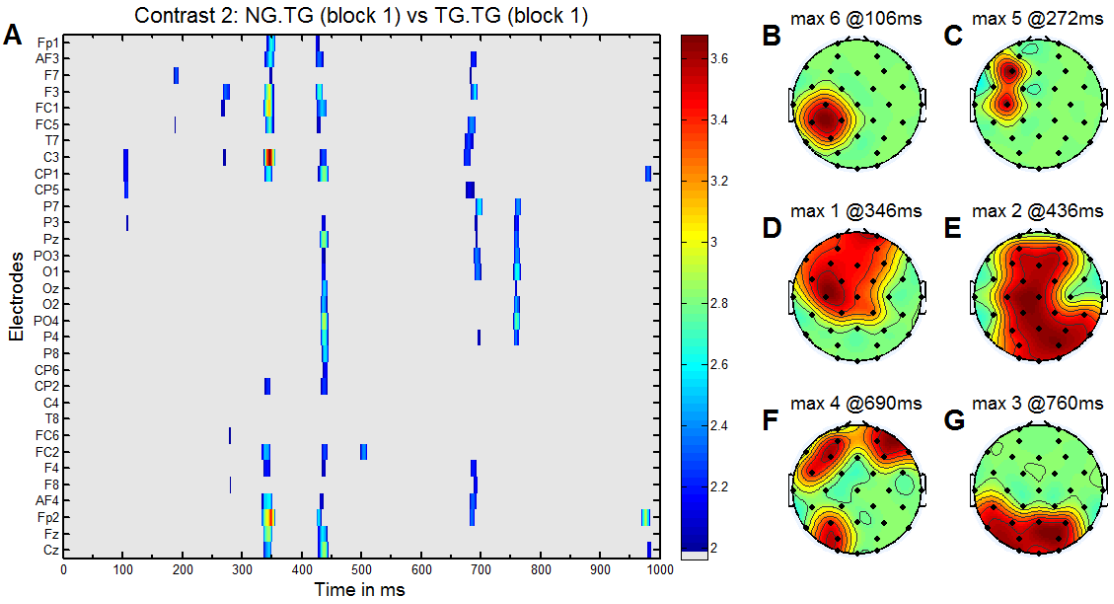


Figure 50 Contrast NG.TG (block 1) vs. TG.TG (block 1). Left: Time vs. Electrodes, colour measures T value amplitude. Right plots: Topographical plot showing local maxima T values. Having the first block, NG is greater than TG around 106 ms (B), 272 ms (C), 346 ms (D), 436 ms (E), 590 ms (F) and 760 ms (G). Note that, the P300 is greater for NG.TG around 346 ms at left fronto-parietal channels. Also, although P300 is greater for NG.TG around 346 ms (D), the negativity around 436 ms (E) for TG.TG condition suggests a different brain process is happening.

4.1.3 Block 2: White noise only

In block 2, ERP differences were explored where S1 was always a white noise stimulus. with both differences between conditions NG.TG – TG.TG and TG-NG. The results of the ERP analysis show the biggest difference in the form of a negative deflection around 200 ms. Bearing in mind this difference and that R2 is significant with linear estimations around this 200 ms, we can analyse linear estimation.

Significant t-values between conditions in the first 1000 ms were found ($p < .05$) in linear estimation with conditions as regressors in block 2, which considers white noise in S1. On the one hand, the topographical plots shows greatest t-values for TG from -268 ms, 976 ms, 228 ms, 180 ms, 702 ms and 508 ms (Figure 51 B, G, D, C, F and E respectively) and greatest values for NG from 328 ms, 158 ms, 732 ms, 788 ms, 298 ms and 130 ms (Figure 52 E, C, F, G, D and B respectively). Therefore, in comparing TG and NG, there appears to be a clear significant difference ($p < .05$) in the mismatch negativity (MMN) in almost all the fronto-central channels for the t-test comparison between TG and NG. Specifically, analysing the other ERP deflections within block 2, ERP differences show for TG a left-temporal and central-parietal greater amplitudes at 180 ms (Figure 51 C) and change to right-temporal at 228 ms (Figure 51 D) informing a possible conflict between a similar signal (left temporal) with some new information (white noise). Additionally, due to the presence of environmental noise, a third peak appeared at 448 ms; due to the peak, RON would not be as strong as it is with environmental noise in block 1. Therefore, due to no clear RON deflection, hypothesis H1 is not supported in block 2.

On the other hand, ERP differences informs fronto-central activations for NG at 328 ms (Figure 52 E) making a P300 but not enough to evoke a P3a or a further RON,. These results in MMN, P300 and no RON waves are consistent with a P3b response when S1 is a white noise. Therefore, due to the fronto-central positive P300 consistent with P3b, hypothesis H3 is supported.

TG also showed a significant (second greatest) activation at 976 ms (Figure 51 G) and a fifth greatest activation at 702 ms and for NG (Figure 51 F) a fourth greatest activation in fronto-central electrodes at 788 ms (Figure 51 G). Bearing in mind the ERPs waves, this would

indicate that when the white noise appears as a novel in S1, S2 would show a greater activation similar to a small MMN (702 ms) with a small P3b (788 ms) and a small RON or different motor response (976 ms).

Context-dependent effects were analysed for white noise in S1, in order to explore the significant difference when the immediately previous event was NG or TG. The ERP deflections resulted in small significant differences for both TG.TG and NG.TG. Although P300 was not one of the six greatest peaks, it was found in the right fronto-parietal around 330 ms biased to NG.TG condition, which supports hypothesis H4. This is different from the results for environmental noise found in the previous block 1.

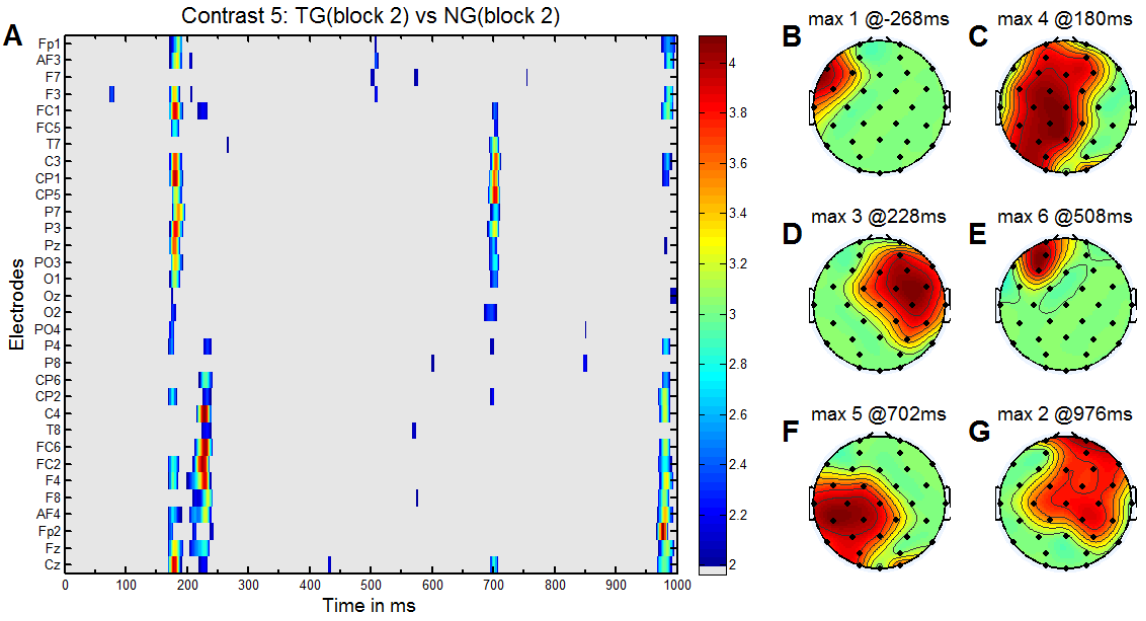


Figure 51 Contrast TG (block 2) vs. NG (block 2). Left: Time vs. Electrodes, colour measures t-value amplitude. Right plots: Topographical plot showing local maxima T values. Having the second block, NG is smaller than TG around -268 ms (B), 180 ms (C), 228 ms (D), 508 ms (E), 702 ms (F) and 976 ms (G). Note that the a kind of expecting ERP wave is different around -268 ms, Ne is not addressed in this work. Note that the MMN is stronger around 180 ms for Novel in NG condition in most of left and central channels.

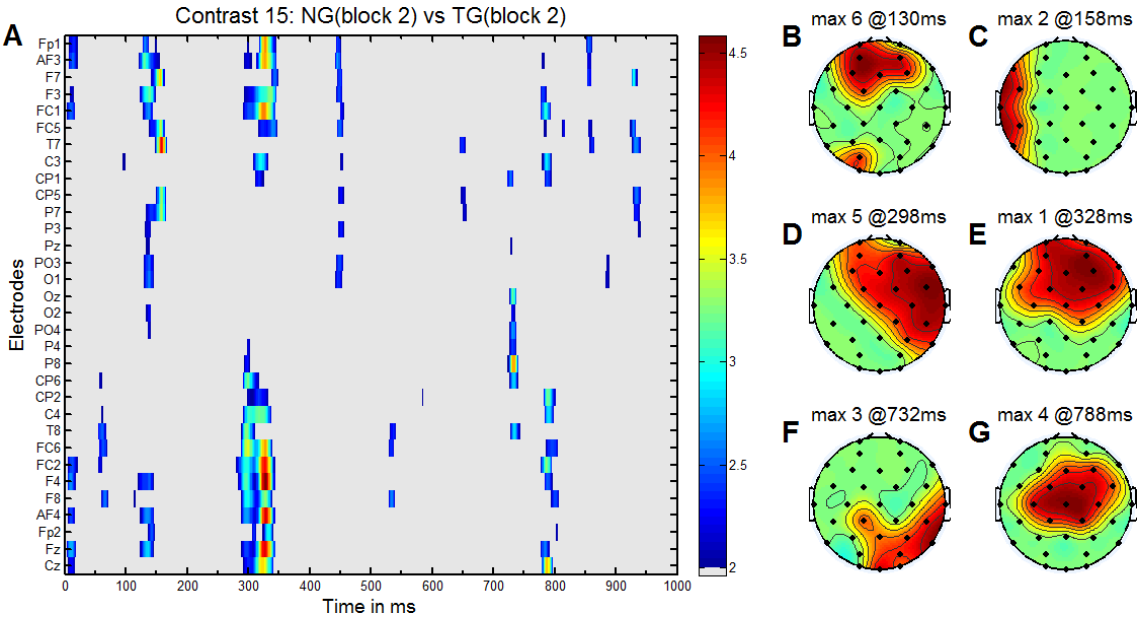


Figure 52 (A) Contrast NG (block 2) vs. TG (block 2). Left: Time vs. Electrodes, colour measures t-value amplitude. Right plots (B-G): Topographical plot showing local maxima T values. Having the first block, NG is greater than TG around 130 ms (B), 158 ms (C), 298 ms (D), 328 ms (E), 732 ms (F) and 788 ms (G). Note that the P300 is stronger between 298 ms (D) and 328 ms (E) and it is evoked in most of the central-right channels. Also, P100 is stronger for Novel in NG condition around 130 ms (B) in frontal channels.

Otherwise, the results for this contrast shows in S2 a bigger significant effect ($p < .05$) at the left-frontal electrodes greater for TG.TG at 788 ms and greater for NG.TG at fronto-central electrodes at 854 ms suggesting that the P300 activation is delayed when the immediately previous context is the NG condition in the goal-driven network. The strongest t-test values for fronto-central electrodes at 1570 ms, possibly reflecting expectancy for the next trial. Although this result is for a single subject, we can state that this result is because order effect (*i.e.* the second block or the sequence favoured block 1 be favoured with distracting trials) or white noise does not evoke a better orienting response than the environmental noise.

4.1.4 Block 3: Environmental noise with scanner background sound

In block 3, the ERP differences in the case that the novel S1 was an environmental noise with the addition of scanner noise as the background sound. Therefore, ERP results with both differences between conditions NG.TG – TG.TG, and TG-NG show a similar big difference around 300 ms, a negative deflection at 200 ms and another negative deflection after 400 ms. Bearing in mind this differences and that R2 is significant with linear estimations, we can analyse linear estimation and find whether this acts as a marker.

Significant F-values between conditions in the first 1000 ms were found ($p < .05$) in linear estimation with conditions as regressors in block 3 which considers environmental noise in S1. The topographical plot shows greatest t-values for TG from 228 ms, 128 ms, 200 ms, 470 ms, 688 ms and 434 ms (Figure 53 D, B, C, F, G and E respectively) and greatest values for NG from 330 ms, 290 ms, 378 ms, 148 ms, 640 ms and 20 ms (Figure 54 E, D, F, C, G and B respectively). Therefore, it appears there are significant differences in MMN moving from frontal scalp activation at 200 ms up to central-parietal activations at 228 ms (Figure 53 C and D), a possibly central negative deflection around 434 ms up to a central-parietal deflection at 470 ms in the RON wave (Figure 53 E and F). These results in MMN, P300 and RON are consistent with orienting of attention when S1 is an environmental noise with the scanner background noise possibly affecting processing in P300. This supports hypothesis H1 for all blocks and H2 for the environmental noise. It did not indicate a significant difference in the second stimulus, which may be explained by the presence of the scanner background noise.

Apparently scanner background noise has a strong effect for the first 200 ms for the goal

sound S2 either for TG (688 ms = 188 ms for S2 Figure 53 G) or NG (640 ms = 140 ms for S2 Figure 54 G).

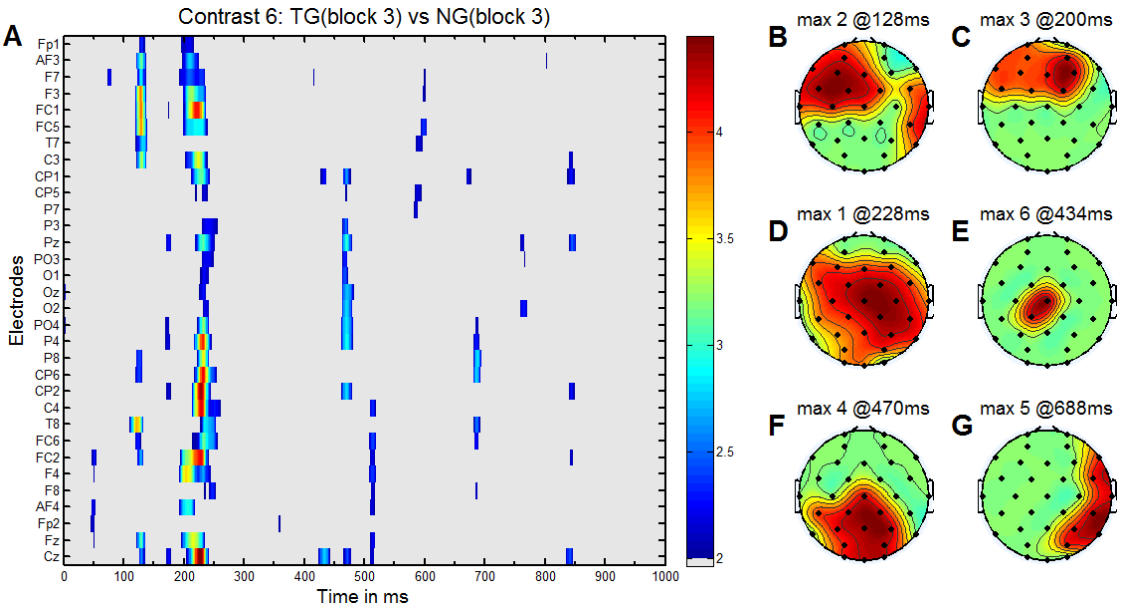


Figure 53 Contrast TG (block 3) vs. NG (block 3). Left: Time vs. Electrodes, colour measures T-value amplitude. Right plots: Topographical plot showing local T value maxima. Having the first block, NG is smaller than TG around 128 ms (B), 200 ms (C), 228 ms (D), 434 ms (E), 470 ms (F) and 688 ms (G). Note that, the N100 for TG condition is stronger for the Tone at left frontal temporal electrodes around 128 ms (B) and MMN for NG condition is stronger for the Novel from frontal 200 ms up to spread activations around 228 ms (D).

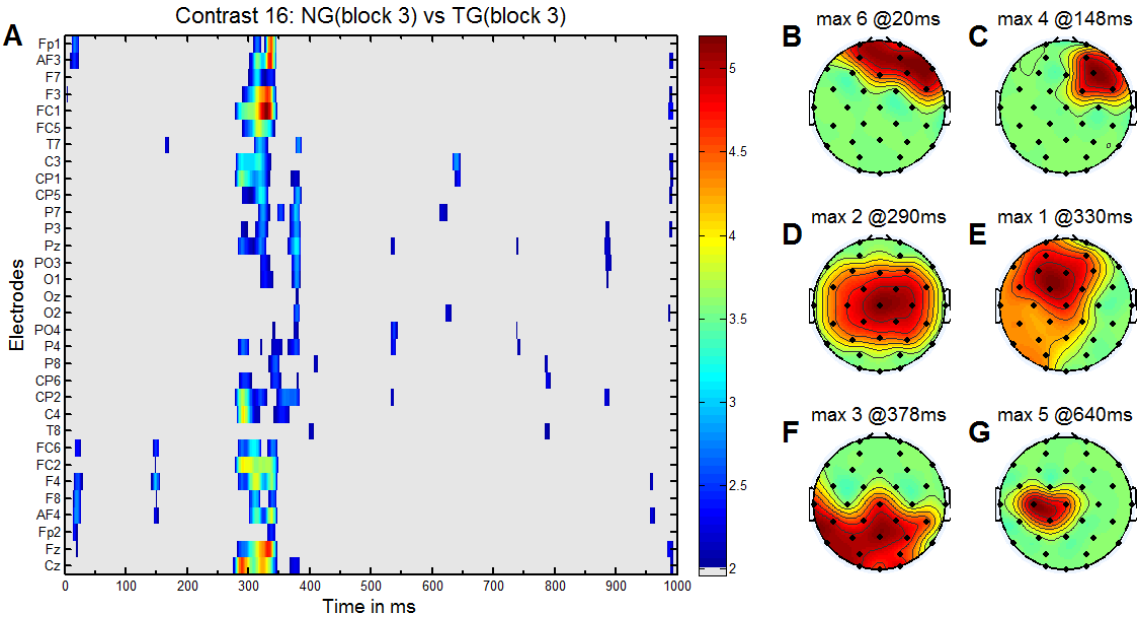


Figure 54 Contrast NG (block 3) vs. TG (block 3). Left: Time vs. Electrodes, colour measures T-value amplitude. Right plots: Topographical plot showing local maxima T values. Having the first block, NG is greater than TG around 20 ms (B), 148 ms (C), 290 ms (D), 330 ms (E), 378 ms (F) and 640 ms (G). Note that the P300 is strongly greater for NG between 290 ms (D) and 378 ms (F) and is evoked in most of the channels. Also, P100 is stronger for the Goal in NG condition around 640 ms (G) is central and right parietal lateralized.

ERP deflections were studied in the context-dependent analysis approach for environmental noise in S1 in the presence of a background sound similar to the scanner background noise, in order to seek for the significant difference when the previous event was NG or TG. The P300 does show a slightly significant greater difference for NG.TG at the right fronto-temporal electrodes at 326 ms, while in the TG.TG condition, the wave is greater at 204 ms resulting in a possible MMN. Therefore, the P300 right lateralized in the NG.TG condition supports hypothesis H4, while the suggested left lateralized bias remains possibly outside P300.

Otherwise, results for this contrast shows a bigger significant effect ($p < .05$) at the left temporal-frontal electrodes for TG.TG than for NG.TG at 2150 ms and inversely at 2410 ms. This is possibly reflecting expectancy for the next trial in a background noise and this would enforce the idea of the expected upcoming TG trial (Hypothesis H4) complementing the left lateralized bias outside the P300.

In contrast to the results without the background noise (block 1), the ERP orienting response is not shown for the immediately previous context, possibly because the scanner background noise is altering the sound processing.

4.1.5 Block 4: White noise with scanner background noise

In block 4, ERP differences occurred in the case where the novel S1 was a white noise in the presence of scanner background noise. Therefore, Figure 55 shows ERP results for trials, with both differences between conditions NG.TG – TG.TG (green lines), and TG-NG (red lines). Results of the ERP difference show smaller differences around a negative deflection at 200 ms, positive deflection around 300 ms and a negative deflection around 400 ms. Bearing in mind these differences and that R2 is significant with linear estimations around this 200 ms, we can analyse linear estimation.

Significant t-values between conditions in the first 1000 ms were found ($p < .05$) in linear estimation with conditions as regressors in block 4, which considers environmental noise in S1. Topographical plot shows greatest F-values for TG from 218 ms, 128 ms, 576 ms, 100 ms, 420 ms and 260 ms (Figure 56 C, B, G, B, F and E respectively) and greatest values for NG from 324 ms, 144 ms, 296 ms, 392 ms, 360 ms and 866 ms (Figure 57 D, B, C, F, E and G respectively).

Apparently scanner background noise makes an inverse effect over the first 200 ms perceptual times for sounds: S1 (100 ms and 128 ms) and goal sound S2 either for TG (702 ms ≣ 202 ms for S2, Figure 56 A) or NG (parietal right lateralized866 ms ≣ 366 ms for S2, Figure 57 GG). This interpretation leads to a P3b activation that did not appear clearly without the SBN (i.e. in block 2).

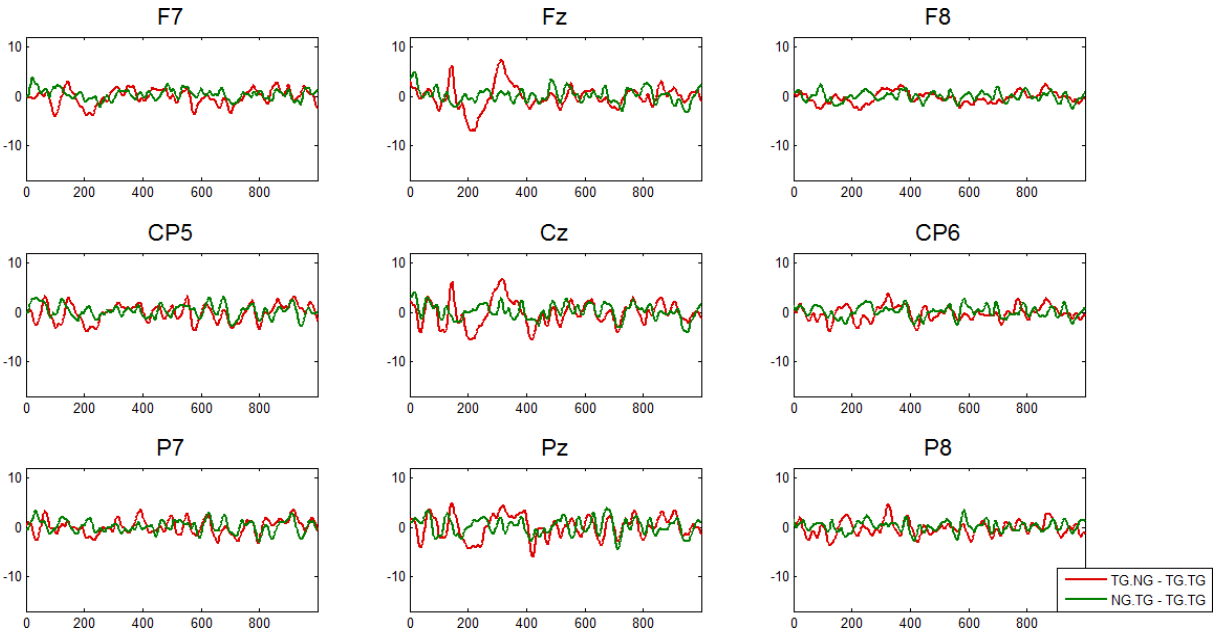


Figure 55 ERPs subtractions in block 4 (white noise) for TG.NG - TG.TG (red lines) and NG.TG - TG.TG (green lines) in several frontal (F7, Fz and F8), central (CP5, Cz and CP6), and parietal (P7, Pz and P8) channels. Note that subtraction shows clear frontal, central and parietal ERPs differences for the typical TG.NG – TG.TG under CTOA = 500 ms. Note that for the difference TG.NG – TG.TG has different P1, MMN, P300 and RON.

Therefore, when comparing TG and NG, a small significant difference ($p < .05$) in the mismatch negativity (MMN) was found in almost all the fronto-central and right parietal channels around 218 ms (Figure 56 D), and in the RON wave in the central-parietal and right temporal electrodes around 420 ms (Figure 56 F). On the other hand, the ERP differences suggest that for NG frontal (298 ms, Figure 57 C), to central-parietal (324 ms, Figure 57 D) and right temporal (360 ms, Figure 57 E) scalp activations, the presence of scanner background noise has altered stimulus processing. Based on these results and the interpretation provided in chapter 2, these small but significant results in MMN, P300 and RON waves are consistent with a P3a response which is reduced in the presence of scanner background noise.

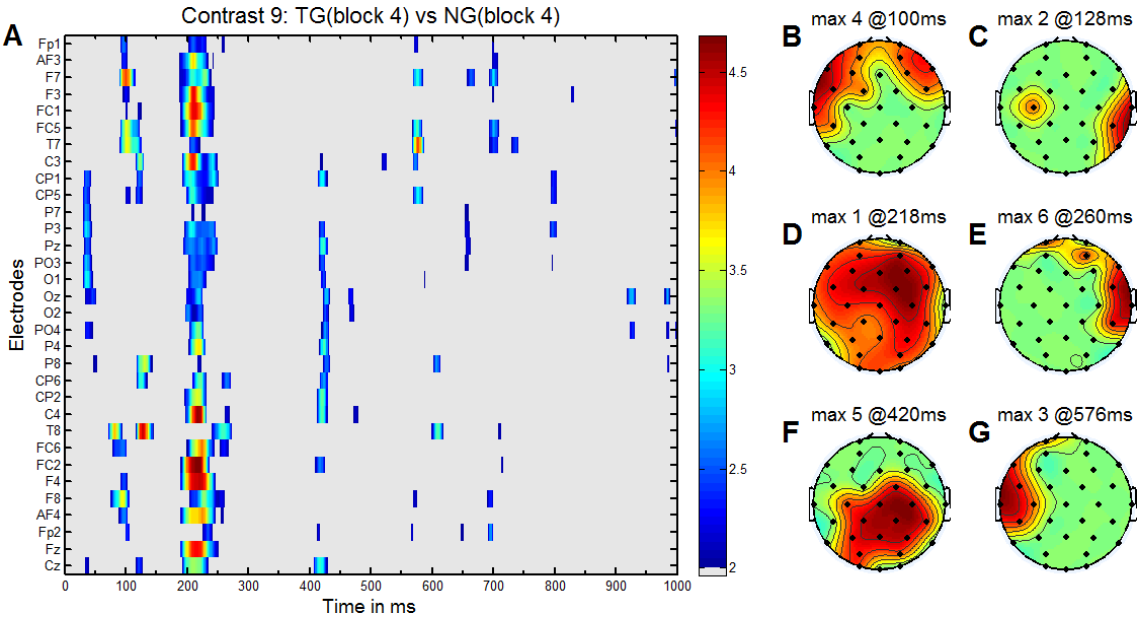


Figure 56 Contrast TG (block 4) vs. NG (block 4). Left: Time vs. Electrodes, colour measures T-value amplitude. Right plots: Topographical plot showing local maxima T values. In the second block, NG is smaller than TG around 100 ms (B), 126 ms (C), 216 ms (D), 260 ms (E), 420 ms (F) and 576 ms (G). Note that the MMN for NG is around 216 ms (D) in almost all the channels but going stronger at right channels around 260 ms (E). Also, RON is stronger for the current Novel in NG condition around 420 ms (F) and it is central and centro-parietal on the scalp.

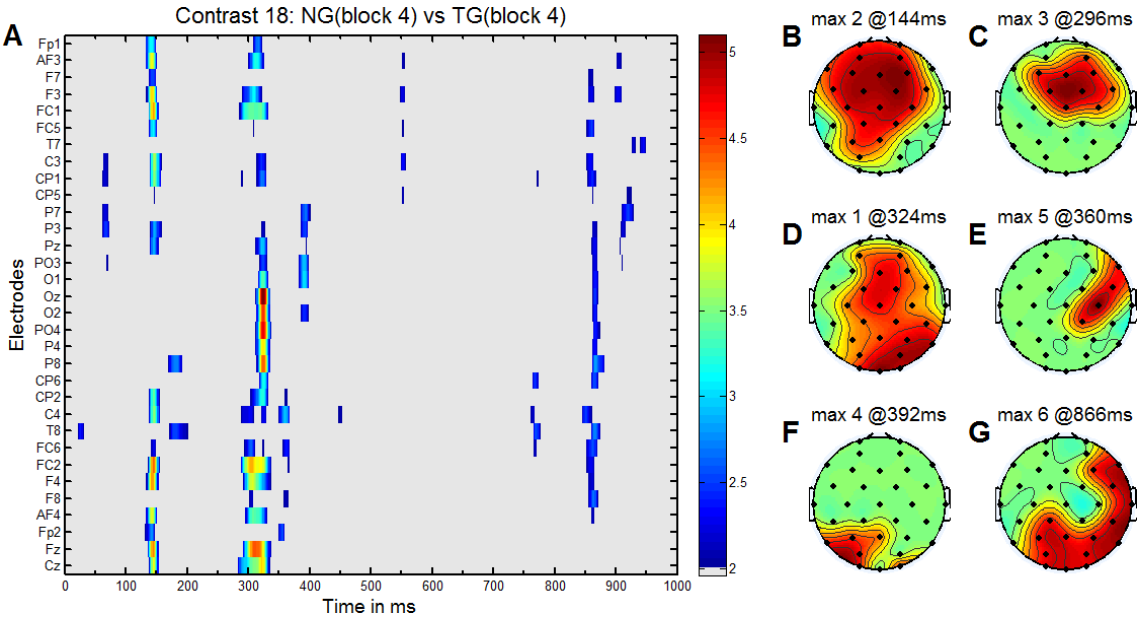


Figure 57 Contrast NG (block 4) vs. TG (block 4). Left: Time vs. Electrodes, colour measures T-value amplitude. Right plots: Topographical plot showing local maxima T values. Having the fourth block, NG is greater than TG around 144 ms (B), 296 ms (C), 324 ms (D), 360 ms (E), 392 ms (F) and 866 ms (G). Note that, for Novel in NG condition: the P300 is stronger between 296 ms (C) and 360 ms (E) and it is evoked in frontal electrodes going to right temporo-parietal electrodes; and the P100 is stronger around 144 ms (B) in most of the channels.

We now seek for ERP waves in the context-dependent approach for white noise in S1 in order to determine the significant difference when the previous event was NG or TG. The P300 did not show a significant difference for both TG.TG (not plotted) and NG.TG (not plotted). Otherwise, results for this contrast shows a bigger significant effect ($p < .05$) in parietal electrodes greater for TG.TG at 718 ms, at the right-central-frontal electrodes greater for TG.TG at 954 ms and greater for NG.TG at 584 ms, and the strongest t-test values for -288 ms right lateralized for TG.TG possibly reflecting expectancy for the next trial.

Overall, for block 4, scanner background noise makes new white noise in the sense that it is a standard noise throughout the experiment. This means that, when comparing the white noise and the scanner background noise in terms of the results set out in Chapter 2, one has to keep in mind frequency and amplitude measures, and in this effect this makes comparison with the immediately preceding event difficult.

Table 15 shows the amplitude and time of each peak in every one of the blocks such as in the 9 channels illustrated in Figure 42. The time window from 300 ms to 400 ms, where we expect to find P300 is highlighted in bold. Although P300 is present in all blocks, in the 9

channels plotted, it is a clear P300 amplitude and time in blocks 1 and 3. It is evident that peaks are consistent similar in time across channels in the first and in the third blocks where the novel noise is the environmental and the difference is the typical between TG.NG and TG.TG conditions.

Table 15

Measure of peak amplitudes in ERP differences TG.NG - TG.TG and NG.TG - TG.TG

								Scanner Background Noise						
Block	1: Environmental sounds				2: White noise				3: Environmental sounds				4: White noise			
ERP diff-	TG.NG - TG.TG		NG.TG - TG.TG		TG.NG - TG.TG		NG.TG - TG.TG		TG.NG - TG.TG		NG.TG - TG.TG		TG.NG - TG.TG		NG.TG - TG.TG	
Channel	A(μV)	t(ms)	A(μV)	t(ms)	A(μV)	t(ms)	A(μV)	t(ms)	A(μV)	t(ms)	A(μV)	t(ms)	A(μV)	t(ms)	A(μV)	t(ms)
F7	4.42	**402**	2.78	190	3.92	856	4.03	88	3.27	**316**	3.11	-202	2.96	144	3.86	22
Fz	12.64	**334**	4.80	**344**	7.62	**326**	5.96	852	8.32	**334**	5.25	122	7.21	**312**	4.88	18
F8	4.29	**338**	1.96	692	3.58	**328**	3.19	846	2.87	**312**	2.68	-56	2.55	862	2.57	94
CP5	5.97	**334**	3.29	106	4.87	160	4.29	240	3.96	**320**	3.61	-200	3.28	64	3.17	676
Cz	13.95	**332**	5.15	436	6.42	**324**	5.22	852	7.61	**292**	4.32	122	6.72	**318**	4.12	16
CP6	6.43	**352**	3.11	-120	4.07	**298**	2.99	-4	3.42	**298**	3.38	624	3.83	**324**	2.91	584
P7	4.74	**334**	3.52	698	4.56	158	4.39	238	4.23	**352**	2.95	-86	3.62	916	3.39	34
Pz	9.50	**330**	5.35	436	3.33	-140	5.44	240	4.68	**318**	3.81	124	5.07	144	3.84	674
P8	3.68	**356**	3.54	-118	3.68	732	4.55	-4	2.75	**340**	3.21	624	4.71	**324**	3.60	584

Values close to the range from 300 ms to 400 ms are highlighted in bold

4.1.6 Discussion

Overall, the results for S1 and S2 in the same trial were: (1) when the novel in S1 is the environmental noise, Scanner Background Noise (SBN) does not attenuate or change the ERP deflections MNN, P3 and RON supporting H1. When S1 is white noise, ERP deflections decrease effect over context, suggesting that SBN destroys the context dependent effect whether or not there is an effect in this context in S2 ; (2) when S1 is the white noise in the presence of the SBN the ERP deflections for S2 are similar to an environmental sound, possibly due to the difference between white noise and the SBN at different phase in time supporting H3; (3) P300 is present in each block in a significantly different way (phase in ERP time and scalp regions) and that explains over all trials the sixth peak found in Figure 45 supporting H2; and (4) P3a is consistent in time and amplitude when S1 is the environmental

noise (shown in Table 15).

When the Novel in the NG condition consists of environmental noise, P100 for Goal stimulus (S2) is larger at the central electrodes for NG condition with the presence or not of the SBN, being at: right lateralized electrodes (shown in Figure 48 around 592 ms) and left lateralized electrodes (shown in Figure 54 around 640 ms).

When the Novel in the NG condition consists of white noise, then in the NG.TG condition a low amplitude complex of P1, MMN, P300 and RON was observed. However, the significance of this complex disappears in the presence of the SBN, leaving positive and deflections instead. Conversely, when the Novel consists of environmental noise, then in the NG.TG condition the low amplitude complex did not appear; however, this complex appeared in the presence of the SBN (see Figure 58) and it is supporting H4.

These results may be explained by considering the presence of the SBN:

- the white noise spectrum when the SBN is substracted, this resulted in a frequency spectrum different to that of the SBN sprectrum and
- the environmental noise when the SBN is substracted, this resulted in a frequency spectrum being qualitatively not different of the SBN sprectrum.

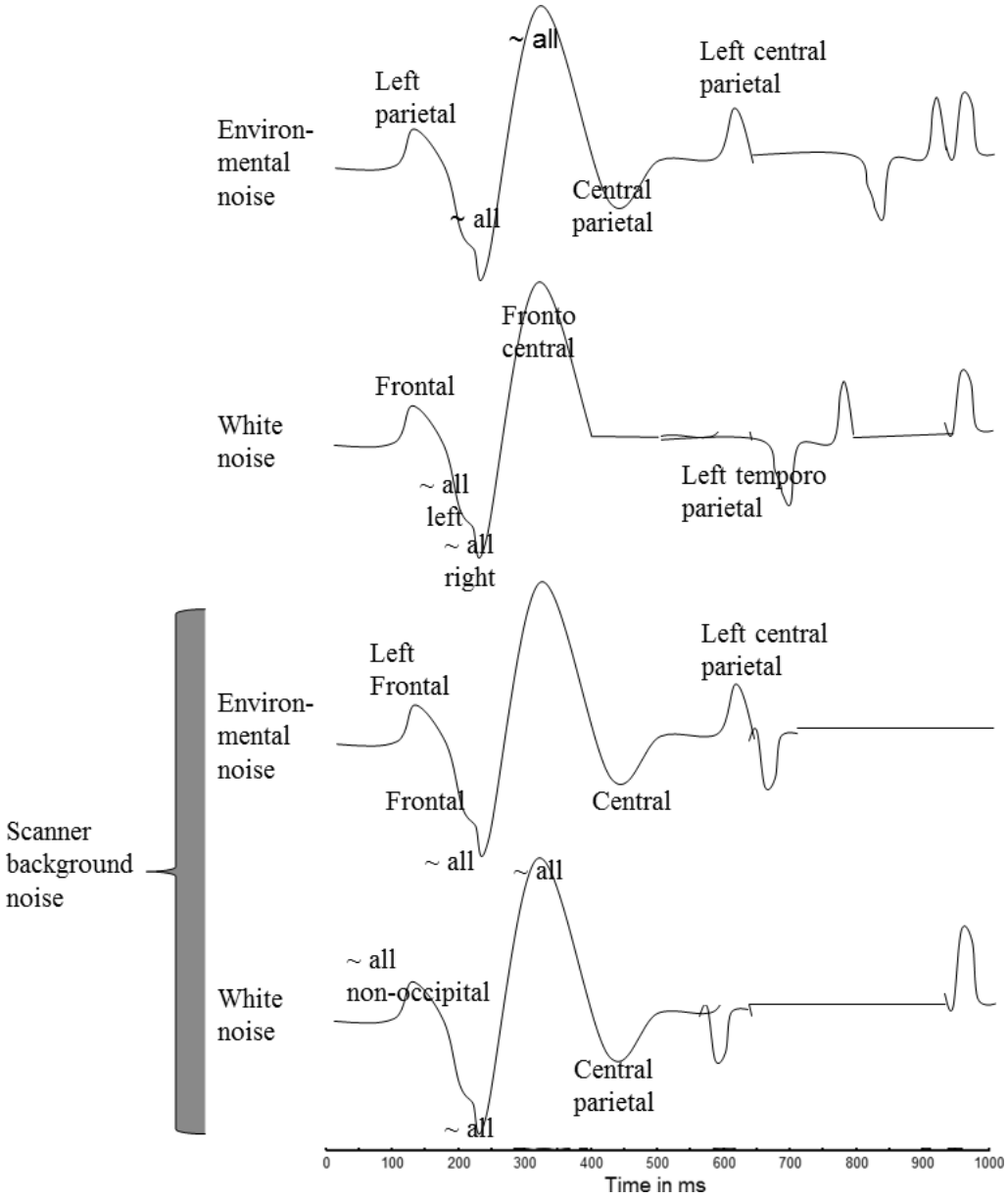


Figure 58 Comparison of the subtraction NG - TG in each block with electrodes that show a significant difference indicated

4.2 Information Theory and States in Orienting Tasks

Bearing in mind the results and discussion of the two main outcomes (contextual analysis and sound properties) of the experiments in auditory orienting attention tasks explored in Chapters 2 and 3, it is important to explain better how these two outcomes are related to the stimulus- and goal-driven networks in a subsequent experiment. Although the pilot

experiment, provided at the beginning of this chapter, allows us to develop a subsequent experiment with environmental noise with some tone frequencies included, it remains unclear what kind of experimental task should be used. Therefore a soft simulation to analyse the sequence of trials and formulate a final experiment design for this work was carried out.

4.2.1 Sequential modelling for input and information estimation.

Lu and colleagues showed that single tones in frequency with durations of between 100 ms and 180 ms are retained in memory for between 0.8 s and 4 s in cortical brain areas. Thus, in 4 participants they found a time constant of around 1.3 s for the left hemisphere and 1.5 s for the right hemisphere (Lu, Williamson & Kaufman, 1992). In other studies, the sound information is considered largely using frequency, intensity and duration (*e.g.* Kanoh, Futami & Hoshimiya, 1996). Therefore, in this analysis of how stimulus properties of the sounds are affecting brain responses, a model based on these time constants was constructed. The modelling considers a simple quantification of memory effects in a sequence of trials, *i.e.* when the time of the last sound through memory process affects the processing of the current sound. For example, 2.1% (left hemisphere) to 3.6% (right hemisphere) of a sound is remembered after 5 s. However, only 0.05% (left hemisphere) to 0.13% (right hemisphere) of the sound is remembered after 10 s.

Here, similar to the Number of States considered for a molecules in a gas model, it is proposed that the memory effect can be treated as the number of states (*NumberStates*) at a time $t_{(i)}$ changes depending on the memory function of the previous effect in from $k = 1$ to $k = i$ in a negative exponential relation (similar to a capacitance discharge) using the time constant τ according to equation 1, where an instantaneous Event(i) contributes to the NumberStates considering a negative exponential memory at the time t(i).

$$NumberStates(t_{(i)}) = \sum_{k=1}^{i} Event(i).e^{\frac{t-t_{(k)}}{\tau}} \qquad \text{Equation 1}$$

Now, we can insert into the equation 1 the quantitative approach of entropy related with expected (Standard cues) and unexpected results (Novel cues). The time constant (τ), bearing in mind Lu and colleagues findings, to the left hemisphere τ_{left} = 1.3 s or to the right hemisphere τ_{right} = 1.5 s , t(i)<t. Initially this is going to be used to validate the power of these assumptions of events as possible predictors of the NumberStates, and taking into account events '*j*' of all the '*i*' events that are relevant for the task in a summation shown in the equation 2, where the Event is not necessarily instantaneous a may have a particular function at the time Event(j,t)

$$NumberStates(t_{(i)}) = \sum_{j=1}^{i} Event(j,t).e^{\frac{t_{(i)} - t_{(j|EventType(i)=EventType(j))}}{\tau}} \qquad \text{Equation 2}$$

Now, equation 2 considers a measure of the time in the event being analysed. In the case of short durations, in the range going from 50 ms to 300 ms, this range of duration is considerably shorter than 1500 ms to 3000 ms between events in different trials used in the different experiments reported here, i.e. at least five times shorter. Therefore, considering that the time in the trial is too short to make changes in the *Event(j,t),* by removing time in the case of short stimuli we have Equation 3:

$$NumberStates(t_{(i)}) = \sum_{j=1}^{i} Event(j).e^{\frac{t_{(i)} - t_{(j|EventType(i)=EventType(j))}}{\tau}} \qquad \text{Equation 3}$$

The time difference $t_{(i)} - t_{(j|EventType(i)=EventType(j))}$ is constant in the case of a sequence where time between two stimuli in the same conditions (CTOA) is the same. For example, CTOA = 300 ms used in the experiment in Chapter 2 or the CTOA = 500 ms used in the pilot experiment here. Therefore, we would consider the previous event whether there is the cue or the novel. Following this, in the equation 3, the number of states can be described as in Equation 4 that is the equation we may use for estimate possible scenarios in an experiment.

$$NumberStates(t_{(i|event(i)=target)}) = \sum_{j=1}^{i} Event(j).e^{-\frac{CTOA}{\tau}} \qquad \text{Equation 4}$$

4.2.2 Simulations and results

Therefore, using the equations 2 and 4 as the basis for the Number of States and CTOA analysis,we can plot the number of states and the variation of the Number of States

according to the stimulus sequence. Simulations have considered: a single CTOA in the NumberStates and this was tested in 19 CTOAs between 150 and 1000 ms, a weight of 8 times for Novel Events compared to Standard Events, sampling time of 10 ms, 600 trials for each CTOA, and using around 3.8 s for the time between trials. Moreover the average if several simulations having a central distribution and a small standard deviation produced similar results. Results of these Number of States changes defined by the sequence are plotted against the CTOA and the number of Novel Trials (plotted in Figure 59). Results pointed to a "saddle indentation" between 300 and 400 ms and with more than 60 trials. From the "saddle indentation":

> Having more than 60 Novel Trials in the design ensures that the experiment will have sufficient change Number of States to give the "saddle indentation" around 300 ms.
>
> The number of possible sound properties may be reduced in order to determine what is the degree of importance of both the sound properties and the variability of conditions in the processing when the change of Number of States is inside the "saddle indentation" highlighted in yellow (lower part of Figure 59).

An important view of these results is that a single CTOA may be in one manifold (e.g. our "saddle indentation") and conclusions and interpretations may change without this view. Therefore, in order to assure empirical comparison it is recommended to have at least two time domains in CTOA to look at the processing of the auditory event without considering the number of states given by memory effects.

4.2.3 Discussion

In this work, an approach for information theory was proposed based on the results of the

previous experiment in this dissertation and the outcome of MEG for auditory memory experiment. This allowed characterizing how the information is managed in lower cognitive level (around 100 ms) when a new auditory experiment is designed. More interesting a bottom line of at least 60 trials and a CTOA reference was found.

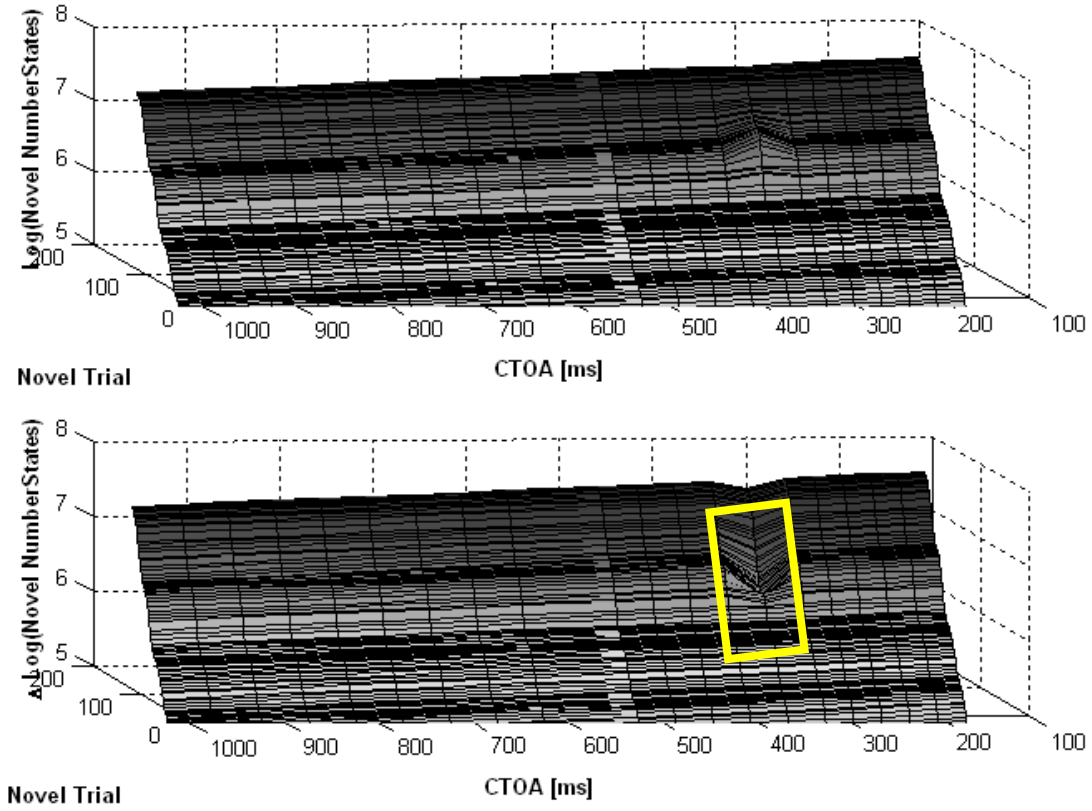


Figure 59 Simulations results for a logarithmic measure of the number of Novel Trials when CTOA is constant in the simulation. Values for CTOA are from 150 ms up to 1000 ms. The saddle indentation is highlighted in yellow.

Indeed, further work to do is to introduce this idea in Gaussian sensory likehood an use prior distribution to concatenate better the memory effects. For example multisensory perception was used to characterize conflicting cue (Natarajan, Murray, Shams, & Zemel, 2009), but the present author did not found in the literature the analysis of the CTOA, number of novel trials and theory of information.

4.3 Design of an experiment to study Orienting Tasks

Thus, the series of analyses can be summarized as shown in Figure 60: In Chapter 2 for CTOA = 300 ms, the differences between schizophrenic patients and controls could be explained by considering the stimulus properties to explain group differences in Novel or Tone followed by the Goal/Novel (Figure 60.A). This design leads to several effects according to the simulation results carried out in section 4.2. Second, the following experiment using fMRI in controls to suggest that the simultaneous Novel and Goal (NG) evokes brain areas concordant with the literature in control of attention when the participants are slower with the presence of the Novel (Figure 60.B). Third, the pilot experiment at the beginning of this chapter with CTOA = 500 ms, where the results points to clear P3a in

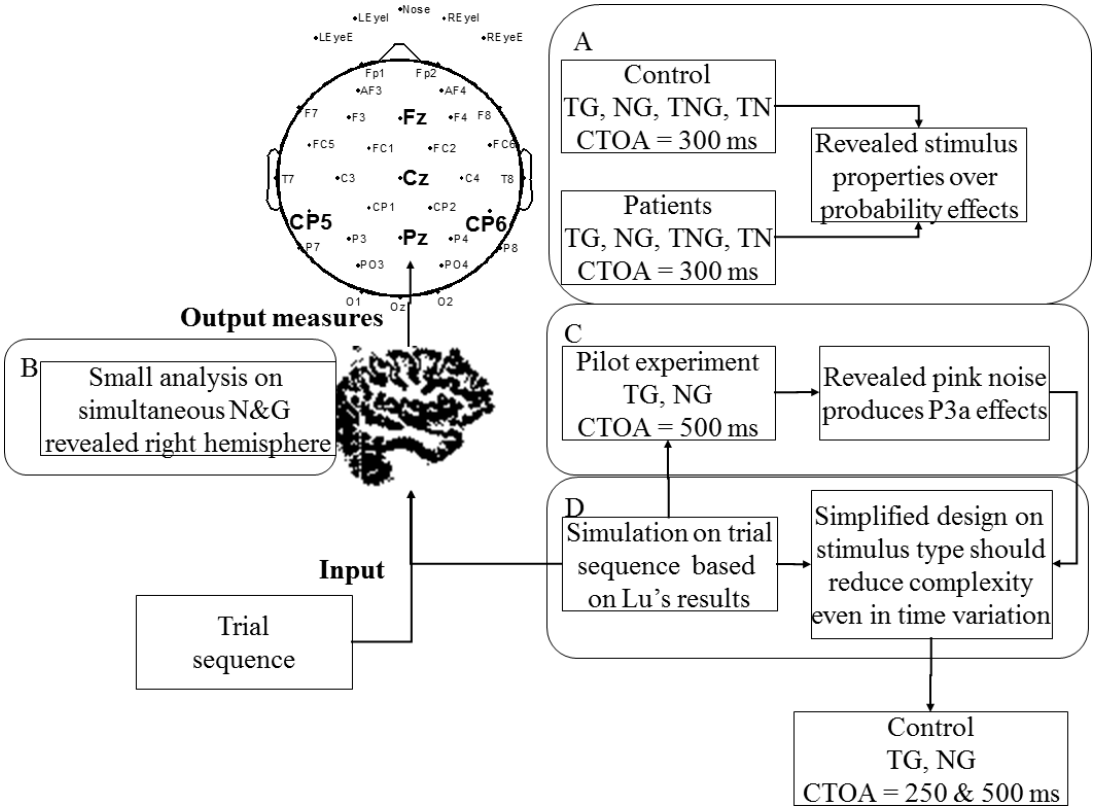


Figure 60 Schematic of the different analyses carried out: A) EEG study in control and schizophrenic patients with CTOA = 300 ms, B) fMRI study in slower participant for simultaneous Novel and Goal condition, C) EEG pilot experiment with CTOA = 500 ms, and D) Simulation of a sequence of stimuli. At the lower part of the figure, the next analysis is suggested to compare different CTOAs such as 250 ms and 500 ms.

amplitude and time using environmental sound as Novels (Figure 60.C). In contrast to the CTOA = 300 ms, the CTOA = 500 ms in the present experimental design does not occur at the time of the "saddle indentation" and this experiment reported some different results for both kinds of sounds but with less than 60 novel trials per condition. And fourth, the time constants to model low level input process in the brain using more than 60 Novel Trials and at least to different CTOA to study whether sound properties are really biomarkers (Figure 60.D).

4.3.1 Novel stimuli design

Although we used less than 60 novel trials per block in the pilot experiment at the beginning of this chapter with CTOA = 500 ms, the results points to clear P3a in amplitude and time using environmental sound as Novels. In this section we are going to address the sounds used and how we can parameterise subsequent experiments.

First, we have used the almost white sounds which have spread frequencies along the time axis. Thus, for example Figure 61 shows the spectrogram of the different sounds. These spectrograms illustrated how at every time point (in seconds) in the horizontal axis the frequencies are spread in the vertical axis. In Figure 61.A the difference with a typical white noise is that before 10 ms there appeared a portion of the sound with different amplitude. Therefore, these kinds of spectrogram possibly produce the same answer in a long experiment, as shown in experiments 1 and 3. On the other hand, we have used the environmental sounds which are different along the time axis and there are also different properties in these different sounds. Thus, for example Figure 61.B shows the spectrogram of the sound new28a.wav. The frequencies are changing along the time presentation, being strongest around 80 ms with a spread changing frequency. Also, around the first 2 kHz, the frequency is stronger all the time and the frequency content is strongest around 1 kHz.

Therefore we design sounds having a pink noise to give some frequency variability along the time and a frequency content joined to that sound. With this we can produce different frequency spectrum at each point in time with a different baseline across time. In this way, Figure 61.C shows the spectrogram of the sound Fp31d100fr31m14.wav. This spectrogram illustrates how at every time point (in seconds) in the horizontal axis the frequencies are spread along the vertical axis, similar to the environmental sound, but this time the frequencies are not changing in a pattern along the time presentation. Also, we have 1.1 kHz; the frequency is strongest all the time allowing a clear parameterisation of the sound in terms of duration and frequency.

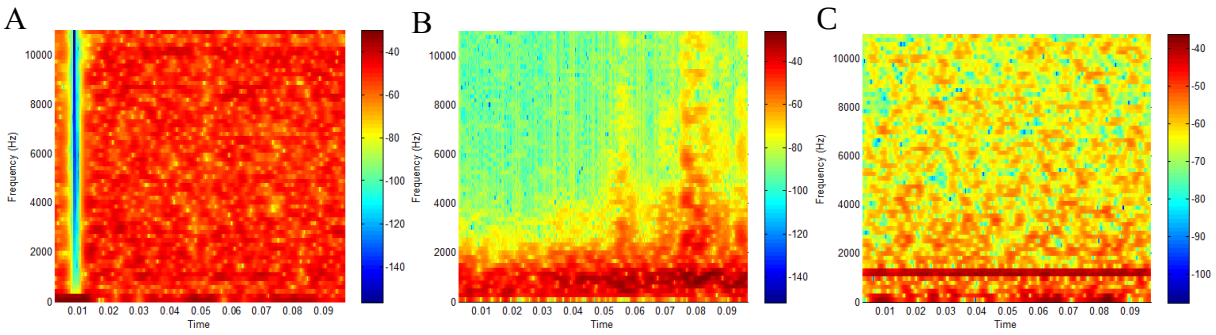


Figure 61 Spectrogram for sound A) N03.wav and B) new28a.wav used in Chapters 2,3 and 4 and C) Fp11d100fr11m14.wav made to be used in Chapter 5. A) The spectrogram is similar to a white noise sound except for the negative values before 10 ms, where still is a noise across frequency scale shown. B-C) Note similar pattern in frecuencies smaller than 2 kHz.

4.3.2 Proposal for the design of following experiments

With these results, including the consistency of the ERP waves for environmental noise and the sounds plus some frequencies created that are similar to the environmental noise added to the experiment, we can look at the attention network explained by Corbetta and collaborators (Corbetta & Shulman, 2002), or the context update model explored initially by Donchin (1981), Donchin and Coles (1998) and later emphasised by Geng and Vossell (2013).

Taking into account these results, we can summarise our next experiment as having:

More than 60 novel trials in the design to get a sufficient number in order to observe CTOA effects in the task.

Employ pink noise with frequency tone between 1 an 3 kHz to get similar spectral properties to an environmental noise.

Reduce the number of possible sound properties to find determine whether it is the sound properties or the variability of conditions that produces the findings discussed in Chapter 2.

At least two time domains in CTOA to look at the processing of the auditory event without considering the number of states given by memory effects.

P300 peaks to the EEG durations were implied in the time between the cue and the target and also between trials. Usually, context update is referred to P300 and with this careful design we can study context updating from the point of view of the input signals. Certainly, memory effect affects signal processing in the brain, therefore we are using a time of 5 s of analysis, taking into account the frequency, intensity and duration of the sound.

5 PARAMETRIC DESIGN AND STUDY OF CONTEXT AND TIME EFFECTS IN REORIENTING OF ATTENTION IN AN AUDITORY ATTENTION TASK

5.1 Introduction

Throughout this research the aim has been to improve our understanding how distraction (orienting to novel stimuli) affects decision making (number parity decisions). The studies described the role of the properties of the stimuli in a random sequence of events (Chapters 2 and 3), and proposing handling Cue-Target Onset Asynchronous (CTOA) in at least 2 levels (Chapter 4). In chapter 4, simulations suggested that CTOAs of between 200 and 300 ms result in the same stimuli containing different amounts of auditory information input than those at CTOA of more than 350 ms are used. In addition, when the CTOA is 500 ms, as in the pilot experiment in chapter 4, this allowed easier visualisation of MMN, P300 and RON ERPs for Novel cues.

Thus, in chapter 4, an experiment was proposed with CTOAs of 250 ms and 500 ms. On the one hand, when CTOA is less than 250 ms, as reviewed by Wright and Ward (2008), exogenous stimuli can create orientation of attention. On the other hand, when CTOA is around 500 ms, as reviewed by Wright and Ward (2008), exogenous stimuli have less effect on the orientation of attention.

Moreover, bearing in mind the ERP research in the literature, several studies led by Näätänen reported that the higher frequencies and shorter duration of the sounds the greater the amplitudes of the MMN generated (Pakarinen, Takegata, Rinne, Huotilainen & Näätänen, 2007). In chapter 4, our analyses of stimuli showed clear MMN, P300 and RON when new sounds are environmental sounds. Although this result involved just one participant and the stimulus properties were not considered, the simulations and further analysis suggested the

possibility of studying the properties of the defined frequency noise inserted on systematic durations of pink noise.

We also can ask whether or not we can be able to test sound properties under prefrontal control, going further than the studies by Näätänen (Näätänen et al. 2012). According to studies by the group led by Koechlin, external stimuli exert a hierarchical control over prefrontal activation levels when stimuli are meaningfully related to the task. In their experiment participants responded to increasingly broader sets of cues that controlled choices including their current context, and the temporal episode in which the task was performed. They made speeded responses to coloured shapes or letters, or withheld a response to a no-go stimulus, on the basis of an instruction cue, which initiated each block. The experiment results indicated a change in the locus of the strongest BOLD signals as a function of broadness of the cueing situation, from premotor to posterior prefrontal to anterior prefrontal. The authors interpreted these findings within a framework that suggested that the lateral frontal lobes are organized as a cascade of control processes mediating sensory, contextual, and episodic control implemented in premotor, caudal and rostral lateral prefrontal cortical regions, respectively (Koechlin et al., 2003). Our studies allow for testing parametrically the influence of the current and context properties in Novel and Standard conditions.

In chapter 3, our findings were influenced by contextual stimulus properties in different ways for controls, but we did not test how a warning cue affects this contextual control. In this chapter (Chapter 5), we ask the question if stimulus properties or time between cue and target will provide a better explanation about the process of distraction in the task. We aim to design not only stimulus properties in a parametric design but also a random sequence in a different spectral resolution for the Novel and Standard conditions. In this way, our contextual approach to analyse allows for the study of additional relationships between

different waves in ERP in individuals and these steps should help to clarify complicated designs such as the 4 different conditions with different kind of sounds and at a single CTOA of 300 ms explored previously (see Chapter 2).

On the basis of the literature reviewed here and previous results, it is clear that the first three experiments were using different CTOAs without a reference CTOA and without a control of the stimulus properties presented to the participant, therefore the present experiment was performed to test the following hypotheses:

H1: Based on the simulations at different CTOAs (described in Chapter 4) and the observed effects of sound properties on P3 amplitude at CTOA = 300 ms (in Chapter 2) and the recent MMN findings (Naatanen et al., 2012), and standard CTOA results (Gonzalves et al., 1999, 2002) it is hypothesized theselective attention is not dependent on the sound properties of the stimuli when CTOA is shorter than 300 ms while it will be affected by CTOAs greater than 300 ms.

H2: Based on the context-dependent and sound properties effects on ERP observed in Chapter 2 as well as on the simulation of the effect of different CTOAs on brain responses (Chapter 4), parametric changes in the sound properties of the stimuli will be used to to attempt to influence the level of prefrontal control on attention. It is predicted that the properties of the current stimulus will be less important than the properties of the stimuli immediately preceding stimuli, or in the case of less frequent stimulus conditions, the previous episode of that stimulus class before the current stimulus.

H3: Different CTOAs on the basis of the simulations in Chapter 4 will be employed and it is predicted that the ERP responses will be systematically affected by the differential time course of attention effects associated wuith exogenous and endogenous stimulus (Ward &

Wright, 2008). Specifically, it is predicted that P300 amplitude will be influenced, as a result of context effects, by the CTOA in the condition immediately before.

H4: Based on our analysis of context dependent effect in EEG in Chapters 2 and 4, the ERP measures of frontal scalp activity will be sensitive to trial by trial contextual effects.

5.2 Methods

Participants.

Twenty healthy adults participated to this study (mean age: 20.29 ± 4.43 years; range 18–31 years). All subjects were free from any history of auditory deficits or known neurological illness. All participants consented to participate in the study. Three healthy participants were excluded because one was using both hands to press buttons and two were changing hands between block, leaving 17 healthy (17 right handed) subjects.

Procedure

Stimuli were sounds presented through insert headphones binaurally at 75 dB sound pressure level. Sounds were stereo at 16 bits and 22050 Hz.

Subjects were asked to perform an odd/even auditory number decision while their scalp EEG was recorded. The paradigm was composed of 720 trials, with trials chosen pseudo-randomly from one of four different conditions: Tone and after a Short time (250 ms) followed by the Goal number (TSG, ~288 trials), Tone and after a Longer time (500 ms) followed by the Goal number (TLG, ~288 trials), Novel and after a Short time (250 ms) followed by the Goal number (NSG, ~72 trials), Novel and after a Longer time (500 ms) followed by the Goal number (NLG, ~72 trials – see table 16).

Table 16

Stimuli combinations for the experiment.

Stimuli name	Number of presentations	Code Processed	Stimuli				
			S1		SOA	S2	
			Type	*Time*		*Type*	*Time*
Tone and after a Short time (250 ms) followed by the Goal	288	TSG	Tone	50 ms	250ms	Number	300 ms
Tone and after a Longer time (500 ms) followed by the Goal	288	TLG	Tone	50 ms	500 ms	Number	300 ms
Novel and after a Short time (250 ms) followed by the Goal	72	NSG	Preceding novel	40-120 ms	250ms	Number	300 ms
Novel and after a Longer time (500 ms) followed by the Goal	72	NLG	Preceding novel	40-120 ms	500 ms	Number	300 ms

SOA: Stimulus-onset asynchrony

Twenty trials were used to introduce the task to the participant.

Each trial consisted of a pair of sound stimuli. The first stimulus (S1) was either a 50 ms standard pure tone cue (~576 trials) or a novel sound with 40-120 ms duration (~ 144 trials). The second stimulus (S2) was presented 250 ms after of S1 onset in the TSG and NSG trials and 500 ms after of S1 onset in the TLG and NLG trials; and S2 was a random number between 1 and 10 (300 ms duration – goal number stimuli). Participants were asked to respond by pressing the button as quickly as possible without sacrificing accuracy. One button was pressed when the number was odd and another button was pressed when the number was even. Hand of response was right across subjects. The Intertrial Interval (ITI) was variable (2100, 2350, 2650 or 3000 ms). The task was presented in 4 separate blocks (180 trials each) with each of the four conditions presented in random order. Within a block, conditions and stimulus sequence were randomly chosen from one of the four conditions for all participants.

EEG Recording

Participants were seated in an armchair in a light and sound-attenuated room with the keyboard placed near to their hands. EEG data were recorded continuously using a passive 64-channel EEG acquisition system (Vision Recorder, Brain Product, Inc., Munich, Germany). The electrode placement followed the international 10–20 system (see *Figure 62*), with a reference electrode at the FCz. Amplified signals were digitized at 5000 Hz with a 16-bit resolution. All electrode impedances were <15 kΩ. Data were band-pass filtered between 0.016–250 Hz during data acquisition. Trials with excessive peak-to-peak deflections, amplifier clipping, or excessive high frequency (EMG) activity were excluded before analysis.

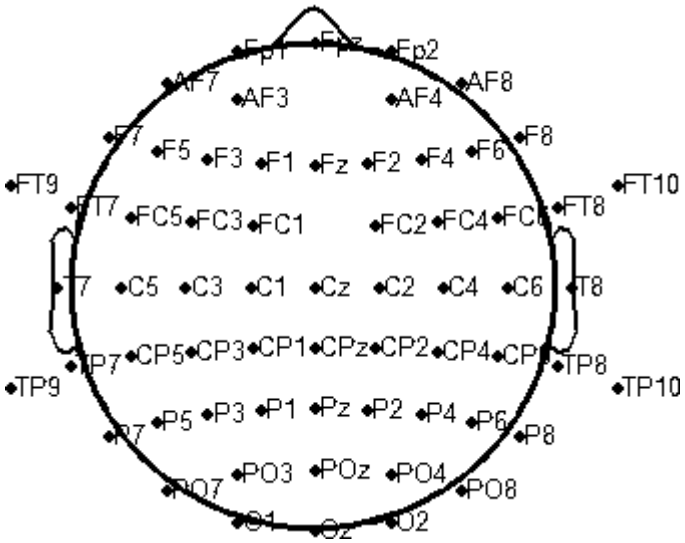


Figure 62 Channels located over the head are shown using the topoplot([],EEG.chanlocs) function of EEGLAB as extending out from the model head borders.

Data Analysis

Goal conditions in this study are the four conditions (TSG, NSG, TLG and NLG). Behavioural data of the 17 participants, with these four factors were first explored through

Matlab functions to plot the mean and variance for the group in each condition as within-group factor.

The reaction times were analysed using a four way analysis of variance (ANOVA) using the ANOVAN Matlab function with goal Conditions and Blocks as the within-group factors. Then a *post hoc* test with multiple comparisons between different Conditions and Blocks was carried out.

Pre-processing was conducted first through Analyzer software (Brain Vision, LLC) to downsample the EEG data from 5000 Hz to 250 Hz. Following this, EEG data were analysed using EEGLAB (Delorme & Makeig, 2004) and Matlab in-house scripts. Eye-movements and artifacts were removed through an independent components analysis (ICA); Data was then filtered with a high-pass at 0.75 Hz and epoched from 300 ms before stimulus onset to 1500 ms after stimulus onset. A baseline correction was then applied. Epochs were then checked for trials with excessive peak-to-peak deflections, amplifier clipping, or other artifacts.

An in-house Matlab script (detailed code is not presented here)was used to calculate the following stimulus properties. The parameters of the sound, local probability and timing measures are given in Table 17. Therefore, 38 parameters were obtained from each pair of sounds S1 and S2:

R(n,1): Fundamental frequency of S1.

R(n,2): Sound duration of S1.

R(n,3): Value of the goal number in S2.

R(n,4): InterStimulus Interval between the end of S2 and the following S1.

R(n,5): Reaction time of the current Goal number.

R(n,6) to R(n,10): R(n,1) to R(n,5) for the previous Novel with the CTOA with an equal value of the CTOA of the current trial.

R(n,11): Number of trials since the previous Novel with the CTOA with an equal value of the CTOA of the current trial.

R(n,11) to R(n,15): R(n,1) to R(n,5) for any previous Novel.

R(n,16): Reaction time of the current Goal number.

R(n,17): Number of trials since any previous Novel.

R(n,18): One, when the previous trial was Novel.

R(n,19): One, when the current trial and the previous trial are Novels.

R(n,20) to R(n,38): Difference of the previous and current trial for the stimulus properties computed from R(n,1) to R(n,19)

The purpose of this analysis was to explore the effects of stimulus properties on the variability of P3a deflection associated with attention and time orienting.

Using LIMO EEG (Pernet et al. 2011), linear modelling with the four conditions was run for all 21 participants. The ERP waveforms were also shown. Due to handiness or fingers used in behavioural answer, 17 participants were used in the rest of the analysis.

Every one of the 38 properties was run as the Continuous Regressors in LIMO to see which stimulus properties are the most significant for this parametric task. Then, linear regression was applied on the 17 participants and the R2 values in time per electrodes were computed and plotted. The 20 maximum R2 values were averaged in every single subject for each

different linear regression run in LIMO with a different stimulus property as a covariate.

Table 17

Sound properties explored on the trials of the experiment.

Property Number	Explanation of the property measured to be taken as a Continuous Regressor in LIMO	Stimulus Group
1	Frequency of S1	Current trial
2	Duration of S1	Current trial
3	Value of the Goal Number	Current trial
4	InterStimulus Interval (ISI) from current S2 to next S1	Current trial
5	Reaction Time	Current trial
6	Frequency of the previous Novel in S1 with the same CTOA	Previous novel CTOA*
7	Duration of the previous Novel in S1 with the same CTOA	Previous novel CTOA*
8	Value of the previous Goal Number with the Novel @ same CTOA	Previous novel CTOA*
9	Previous ISI from S2 to next S1 with the Novel @ same CTOA	Previous novel CTOA*
10	Previous Reaction Time with the Novel in the same CTOA	Previous novel CTOA*
11	Number of trial since the previous Novel with the same CTOA	Previous novel CTOA*
12	Frequency of previous Novel in S1	Any previous Novel
13	Duration of previous Novel in S1	Any previous Novel
14	Value of the previous Goal Number presented with the previous Novel	Any previous Novel
15	Previous ISI from S2 to next S1 of the previous Novel	Any previous Novel
16	Previous Reaction Time of the previous Novel	Any previous Novel
17	Number of trial since any previous Novel	Any previous Novel
18	IF Previous trial was Novel THEN 1, ELSE 0.	Any previous Novel
19	IF the current trial and the previous trial waere Novels THEN 1, ELSE 0.	Any previous Novel
20	Previous Property Number 1 - Current Property Number 1	Context
21	Previous Property Number 2 - Current Property Number 2	Context
22	Previous Property Number 3 - Current Property Number 3	Context
23	Previous Property Number 4 - Current Property Number 4	Context
24	Previous Property Number 5 - Current Property Number 5	Context
25	Previous Property Number 6 - Current Property Number 6	Context
26	Previous Property Number 7 - Current Property Number 7	Context
27	Previous Property Number 8 - Current Property Number 8	Context
28	Previous Property Number 9 - Current Property Number 9	Context
29	Previous Property Number 10 - Current Property Number 10	Context
30	Previous Property Number 11 - Current Property Number 11	Context
31	Previous Property Number 12 - Current Property Number 12	Context
32	Previous Property Number 13 - Current Property Number 13	Context
33	Previous Property Number 14 - Current Property Number 14	Context
34	Previous Property Number 15 - Current Property Number 15	Context
35	Previous Property Number 16 - Current Property Number 16	Context
36	Previous Property Number 17 - Current Property Number 17	Context
37	Previous Property Number 18 - Current Property Number 18	Context
38	Previous Property Number 19 - Current Property Number 19	Context

* Properties for the same CTOA means that the previous properties are from a trial with the same CTOA.

All the single subject results were placed together in a matrix, with the matrix then was plotted to visualise which properties made more significant R2 contribution across most of the participants. Therefore, the plotted matrix showed when one of the stimulus properties was added as a Regressor to the conditions of the task. The first analysis includes TSG and NSG conditions and the second analysis includes TLG and NLG to discover whether the hypotheses are supported. After the stimulus property is identified, for each subject, 38 ANCOVA models were used, having in each ANCOVA: the 4 conditions plus one covariate coding for the stimulus property identified in this study. In this case using a simple hierarchical model of the EEG data with β_i as the constant and S_i y A_5 as the categorical and the continuos regresors following the equation:

$$EEG = \beta 0 + \sum_{i=1}^{4} \beta_i S_i + \beta_5 A_5 + Error$$

Parameters (β-values) were evaluated at every electrode and time point autonomously, yielding a lattice of 63 (electrodes) * 151 (time focuses, from 148 ms to 748 ms in 4 ms steps) for each regressor in short CTOA and 189 (time focuses, from 148 ms to 900 ms in 4 ms. Comparative electrode*time point frameworks were processed for R2, F and p-values for both the linear models and for each regressor (partial F-values).

At the group level, a repeated measure ANOVA was conducted on the parameters computed for each condition. Because sounds properties, local probabilities and other stimulus properties that influenced the P300 were regressed out for each subject/trial, differences between conditions can only reflect differences due to novelty and not differences between stimuli in the different conditions.

5.3 Results

5.3.1 Behavioural analysis

Both accuracy and mean response latencies were examined in the critical trials common to our four goal stimuli conditions (TSG, NSG, TLG and NLG). *Figure 7* shows the mean reaction times in each condition for the participants. Mean per each condition are shown in

bars. The ranges are superposed using one standard deviation.

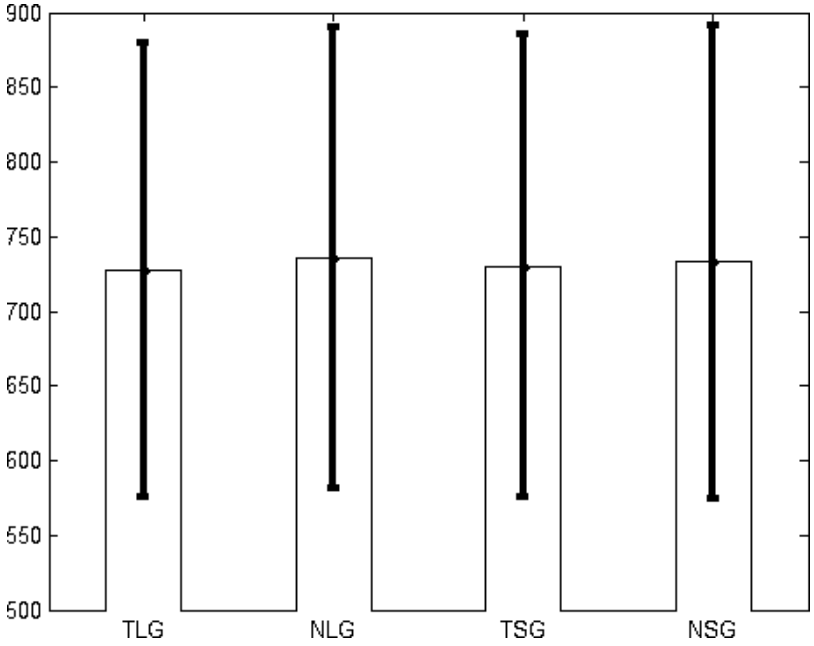


Figure 63 Estimated Marginal Means of Reaction Times (RT) computed at the mean of the reaction time for conditions TLG, NLG, TSG and NSG.

Overall, participants performed well (94.2 % accuracy of goal trials). The proportion of correct responses was analyzed using a three way ANOVA considering Participants, Conditions and Blocks. Although the main effect in the Condition was not significant ($F(3) = 1.32$, $p = .2669$), the main effect in the Blocks was significant ($F(3) = 3.08$, $p = .0263$).

The multiple comparison *post hoc* test did not show overall differences between NSG and NLG Conditions ($F(1) = 0.18$, $p = 0.673$), however there is a significant difference between NSG and NLG Conditions per Block ($F(1,3) = 4.02$, $p = .0073$).

5.3.2 Linear estimation in all participants

Linear regression was applied to the 21 participants. The individual explanation of the variance (R2) of this first analysis is for short CTOA (TSG and NSG conditions) and long CTOA (TLG and NLG). Therefore, these four conditions were considered as the Categorical variables to run the linear regression in LIMO. This analysis enables the visualisation of

whether the linear regression has a consistent significant effect over electrodes and time for most of the participants.

Figure 64 shows the R2 in times per electrodes for three of the 21 participants, and the Conditions were used as the Categorical Regressors, note P03 (on the left) and P05 (on the center) have several R2 > .01 while P06 (on the right) does not have. The 4 participants excluded because they answered in a behaviourally different way to the other participants (with a different hand or different fingers) are also shown. These participants are: number 3 (P06) with an R2 maximum around 0.05, number 7(P12) with an R2 maximum around 0.05, number 9(P14) with an R2 maximum around 0.045, and number 16(P22) with an R2 maximum around 0.06. These R2 values were smaller than the R2 values of the other participants and they were excluded from the present analysis. The pattern over almost all participants shows consistent signatures in electrodes and time.

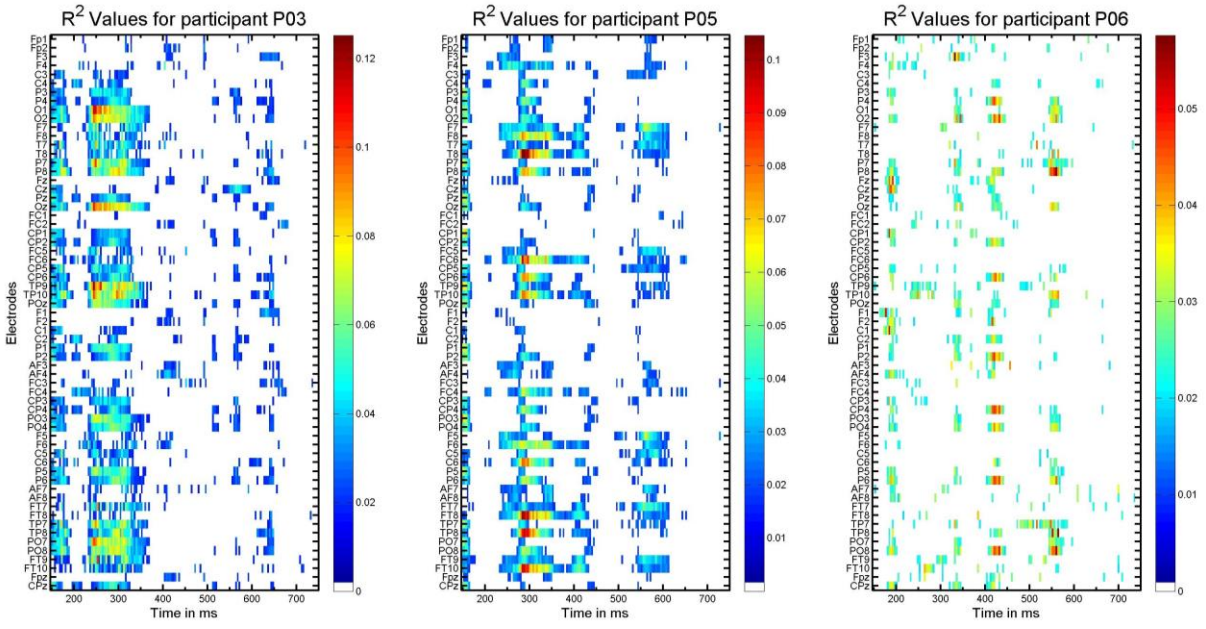


Figure 64 Amplitude of R2 points in time per each channel for three of the 21 participants having Conditions as a Categorical Regressors for TSG and NSG condition after LIMO computation in the range of time from 148 to 748 ms which covers from N100 for S1 up to 500 ms for S2.

5.3.3 ERPs in short CTOA in all the participants

The second analysis includes the short CTOA condition (TSG and NSG) in every epoched EEG dataset per each participant.

Figure 65 shows the grand average ERP waveforms at 9 representative electrodes in the 17 participants. The ERP difference NSG - TSG is shown in dotted lines in red. The TSG is of larger amplitude in frontal channels for P100, N200 and a P300 appears mixed with the P100 of the second stimulus of the Novel stimulus and N200 of the second stimulus.

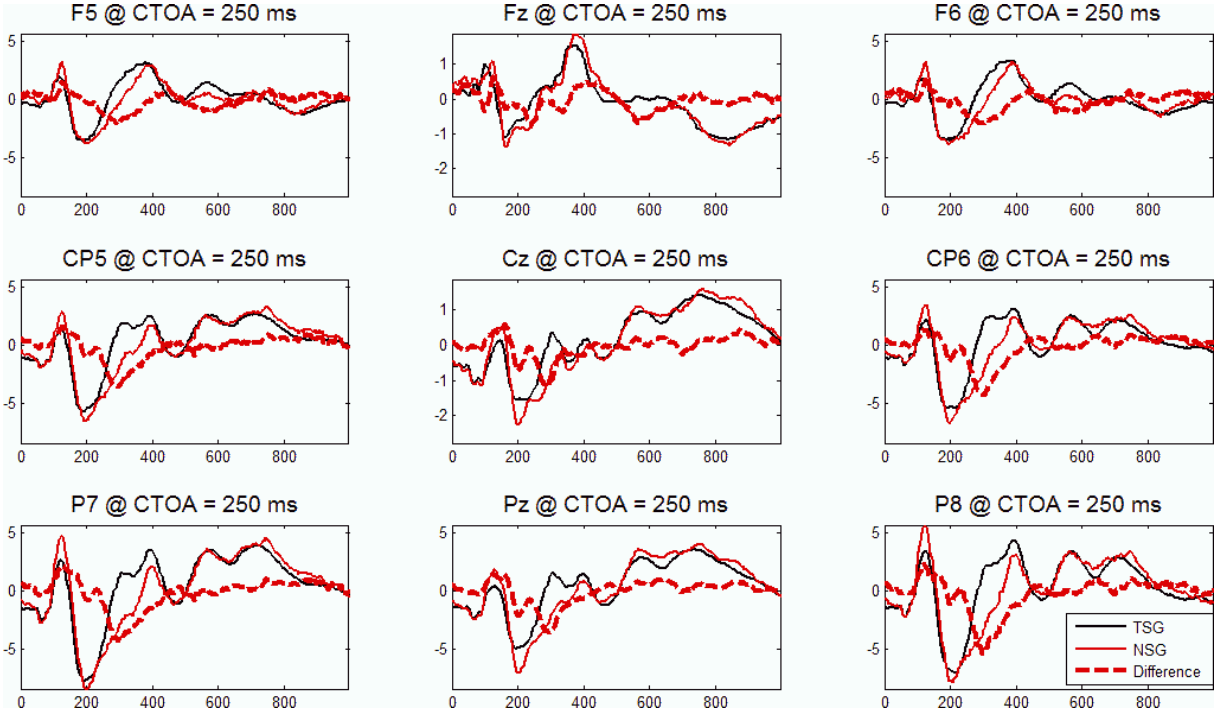


Figure 65 Grand average ERP waveforms at 9 representative electrodes in 17 control participants in the TSG and NSG conditions. NSG minus TSG is shown in dotted lines in red. Vertical blue lines show the beginning of the Goal number. Note that TSG ERP is of larger amplitude in frontal channels for P100, N200 and a P300 appears mixed with the P100 of the second stimulus of the Novel stimulus and N200 of the second stimulus.

5.3.4 Stimulus properties analysis in R2 in short CTOA in all the participants

Linear regression was applied on 17 participants. The individual R2 of this first analysis is

for short CTOA (TSG and NSG conditions). Therefore, only these two conditions were considered as the Categorical variables to run the linear regression in LIMO.

The 38 properties (shown in table 3) were run as the Continuous Regressors in LIMO to see which stimulus properties are the most significant predictors for this double CTOA switching task. From the R2 in time per electrodes, the 20 maximum R2 values were averaged for each regressor (see *Figure 66*). Single subject results suggested that frequency and duration were the strongest factors in predicting the percentage of variance (R2). The second property (duration) was the strongest significant sound property when added as a regressor.

The properties used as regressors introduced significant effects in almost all the participants. However, several of the R2 effects are smaller than 0.05 (*i.e.* less than 5% of the variance). On the other hand, when we measure the percentage of the variance improved by the regressor added to the conditions, the improvement is more than 100% in several cases in regressors 1 (current frequency), 2 (current duration), 19 (previous frequency) and 20 (previous duration).

Analysing the results of the process of the stimulus through ERP waves revealed:

- Sound properties 1 (frequency) and 2 (duration) have the strongest R2, indicating that these properties were activated in most of the participants. This supports hypothesis H1.
- Sound properties 20 (relative change of frequency) and 21 (relative change of duration) are strong properties activated in most of the participants, but they are quantitatively less than the current sound properties. This is support that the context stimulus is important, therefore supports hypothesis H3.
- Stimulus Property 5 (reaction times) have significant R2 in some of the participants,

but not in all of them. Reaction times, then, are not as relevant as the sound properties of the stimulus. This focus is that stimulus driven properties are stronger than goal driven when the cue is changing between Novel and Standard.

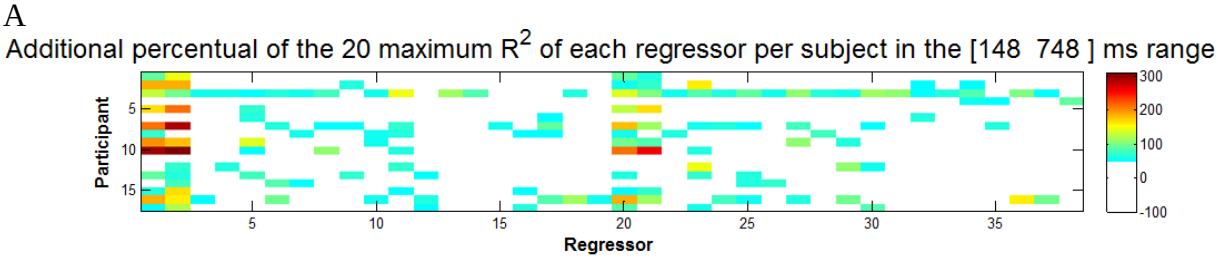
- Stimulus Property 11 (stimulus Novel probability with the same CTOA) is present in some of the participants, but not in all of them. Therefore, stimulus Novel probability is not as relevant as the sound properties of the stimulus and this does not appropriately support hypothesis H4.

- Stimulus Property 17 (stimulus Novel probability)

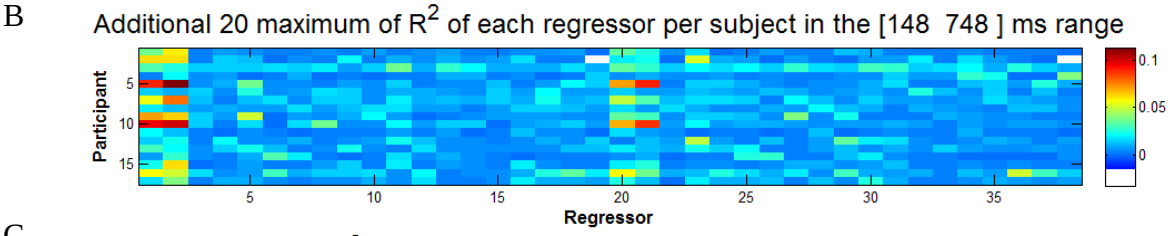
have several participants with significant R2, but not in all of them. Stimulus Novel probability, then, is not as relevant as the sound properties of the stimulus.

- Stimulus Property 23 (relative change of ISI between S2 and next S1) have several participants with significant R2, but not less than the other properties above. Stimulus Novel probability, then, is not as relevant as the sound properties of the stimulus.

A



B



C

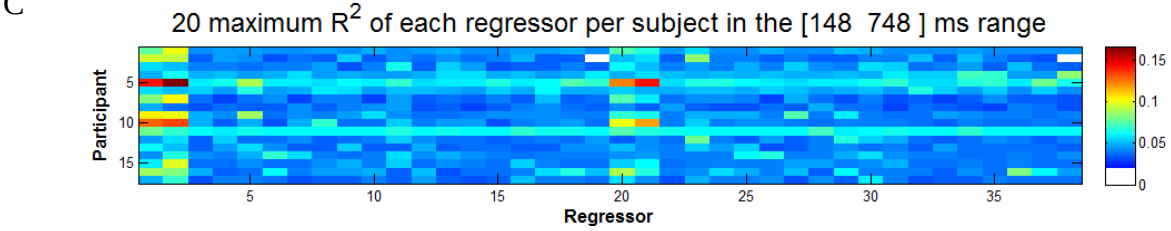


Figure 66 Averaging of the 10 maximum R2 points per each Property (see Table 3) as a Regressor added to the conditions for TSG and NSG condition after LIMO computation (in the range of time from 148 to 748 ms). Amplitude scale is in colours and Regressors are in

the horizontal axis and Participants in the vertical axis. A) Additional percentages of variance (greater than 50%) explained by each Regressor. B) Additional variance explained by the Regressor. C) Variance explained by the Regressor and Conditions. Note that Properties 1, 2, 20 and 21 are the strongest Regressors in most of the subjects.

Given the greatest R2 in duration for the current trial (property 2) and the greatest for the relative change in duration (property 21) as well, we then ran a first level analysis for all the participants with those properties 2 and 21 as the continuous Regressors in LIMO (see *Figure 67*).

Results for the duration and the relative change in duration as the Regressors added to Conditions points to a greater and uniform explanation of the variance through R2. This supports hypothesis H5 about current and context properties in ERP waves. Therefore, this also supports the results and interpretation discussed in Chapter 2, that not only the current trial is influencing the ERP waves but also the previous trial.

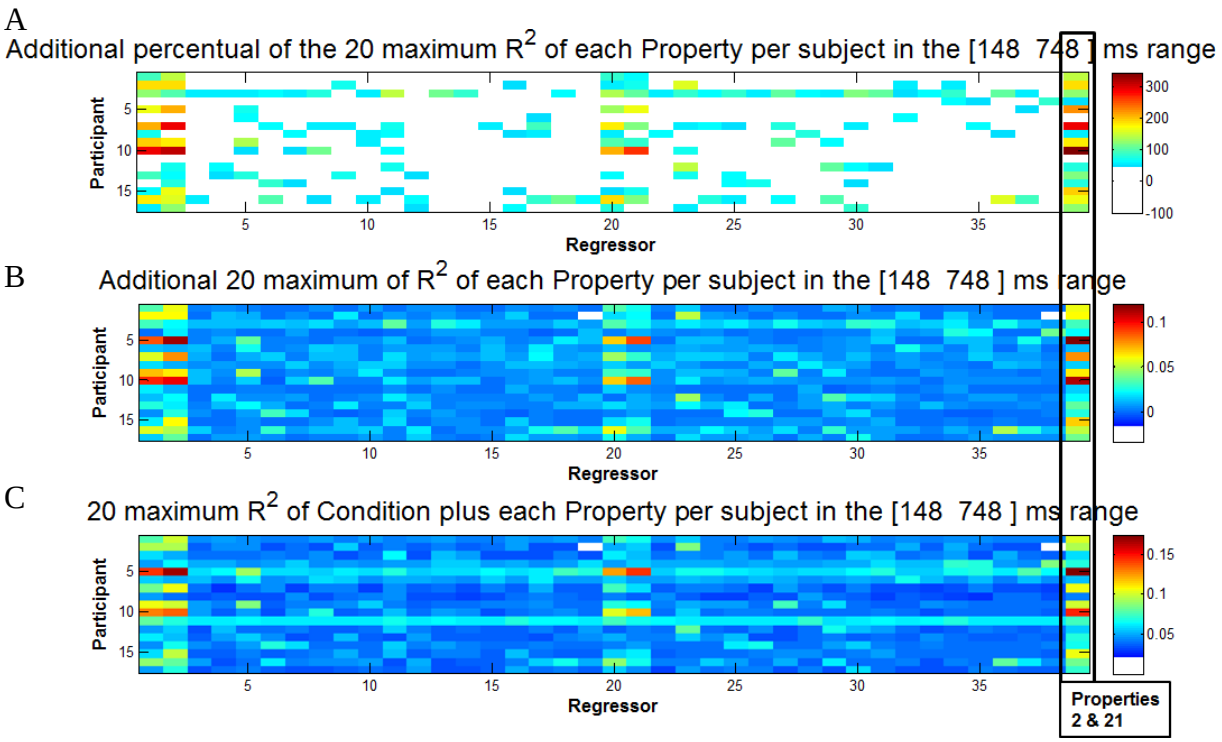


Figure 67 Averaging of the 10 maximum R2 points per each Property (see Table 3 and the Properties 2 & 31) as a/the Regressor(s) added to the conditions for TSG and NSG condition after LIMO computation (in the range of time from 148 to 748 ms). Amplitude scale is in colours and Regressors are in the horizontal axis and Participants in the vertical axis. A) Additional percentages of variance (greater than 50%) explained by each Regressor. B) Additional variance explained by the Regressor. C) Variance explained by the Regressor and Conditions. In the highlighted rectangle on the right, note that the Properties 1 and 20, added as the Regressors, makes the strongest Regressors in most of the subjects.

5.3.5 Second level analysis of short CTOA conditions

Figure 68 shows the Second level T-Test analysis for TSG condition for the 17 participants. Amplitude of T-values points are given by colours in time per each channel for the 17 participants. In the first level Conditions, NSG and TSG were used as the Categorical Regressors for the LIMO computation (in the range of time from 148 to 748 ms). On the right, the topographical plots for the six T-values maxima are shown at 332 ms and 372 ms with bilateral and non-central distributions, respectively, biased to the left (*Figure 68*.D-E). This result is consistent with the exogenous bilateral control of attention (Corbetta & Shulman, 2002) and biased to the left for standard stimulus (Corbetta et al. 2008). There are also negative maxima at 148 ms and 244 ms at the frontal and temporo-parietal electrodes, respectively (*Figure 68*.B-C). This is consistent with the occurrence of N200 before a P300 response.

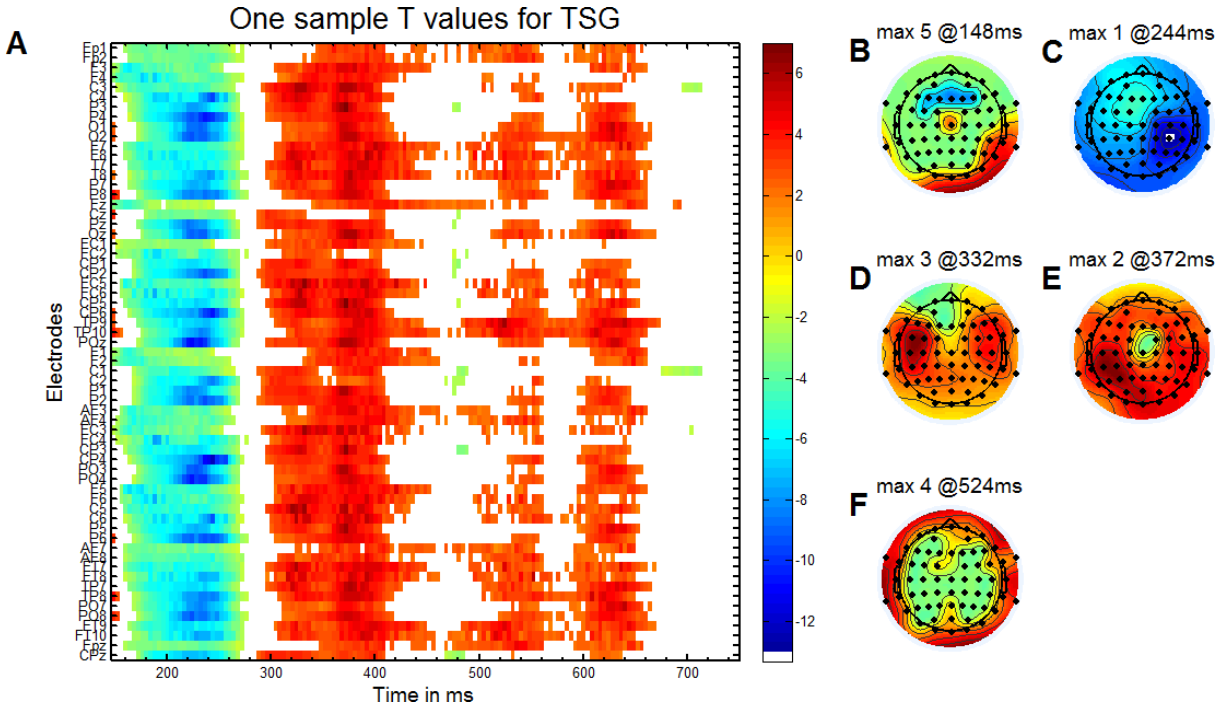


Figure 68 (A) Second level T-Test analysis for TSG condition on the 17 participants. Amplitude of T-values are given in colours at every time per each channel having Conditions TSG and NSG as the Categorical Regressors for LIMO computation ((B-F) in the range of time from 148 to 748 ms). On the right the maximum is shown at (D) 332 ms and with a bilateral distribution.

Figure 69 shows the Second level T-Test analysis for NSG condition for the 17 participants. Amplitude of T-values points in time per each channel at every participant having Condition as a Categorical Regressors for NSG condition after LIMO computation (in the range of time from 148 to 748 ms). On the right, the maximum is negative at 196 ms (*Figure 69*.B) with a more left temporo-parietal and occipital scalp distribution. There is also a maximum as shown from 316 ms, being in 344 ms to 372 ms and with a frontal scalp distribution (*Figure 69*.C-E). This result is consistent with the typical distribution for P3a according to Polich (2007). Subsequently, there is a negative maximum at 436 ms (*Figure 69*.F), which is consistent with a RON wave (Schroger & Wolf, 1998a)

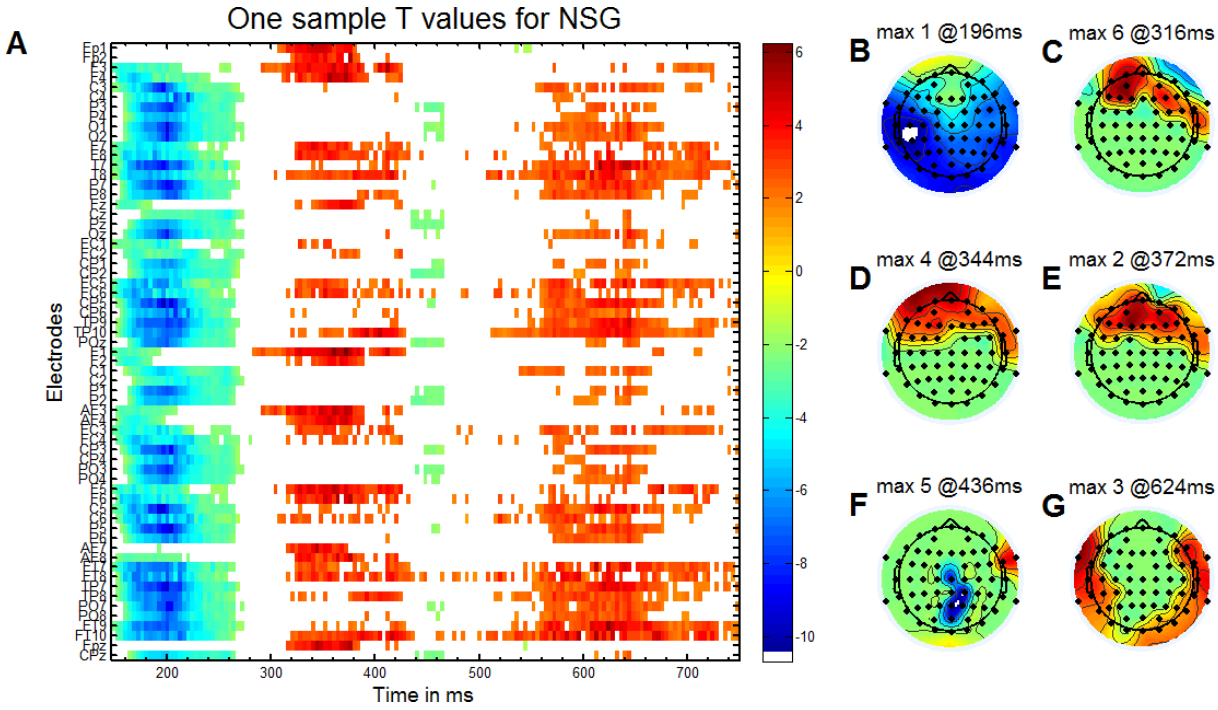


Figure 69 (A) Second level T-Test analysis for NSG condition on the 17 participants. Amplitude of T-values points in time per each channel at every participant having Condition as a Categorical Regressors for NSG condition after LIMO computation ((B-G) in the range of time from 148 to 748 ms). On the right the maximum is shown at (E) 372 ms.

Näätänen's group reported that the higher frequencies and shorter duration of the sounds the greater the amplitudes of the MMN generated (Pakarinen et al. 2007). In *Figure 70* our T-values results showed waves for MMN (negative maximum at 200 ms, *Figure 70*.B) and P300 (negative maximum at 320 ms, *Figure 70*.C). In our analyses, stimuli duration evoke negative T-values MMN and P300 and the maximum is positive at 484 ms (*Figure 70*.E) going for right biased temporo-parietal electrodes, where RON waves should be. Therefore, our results are consistent in MMN with Pakarinen's results, and extend then for P300 and a RON. Possibly the managing of frequency does not allow showing the pattern of RON in ERP results. Therefore the duration results have shown the significant orienting ERP waves.

Therefore, the present experiment has shown that ERPs may represent greater and smaller durations and we may be able to observe the effects of the properties of the defined frequency noise inserted on systematic durations of pink noise. In other words, there is attention control by systematic changes in durations.

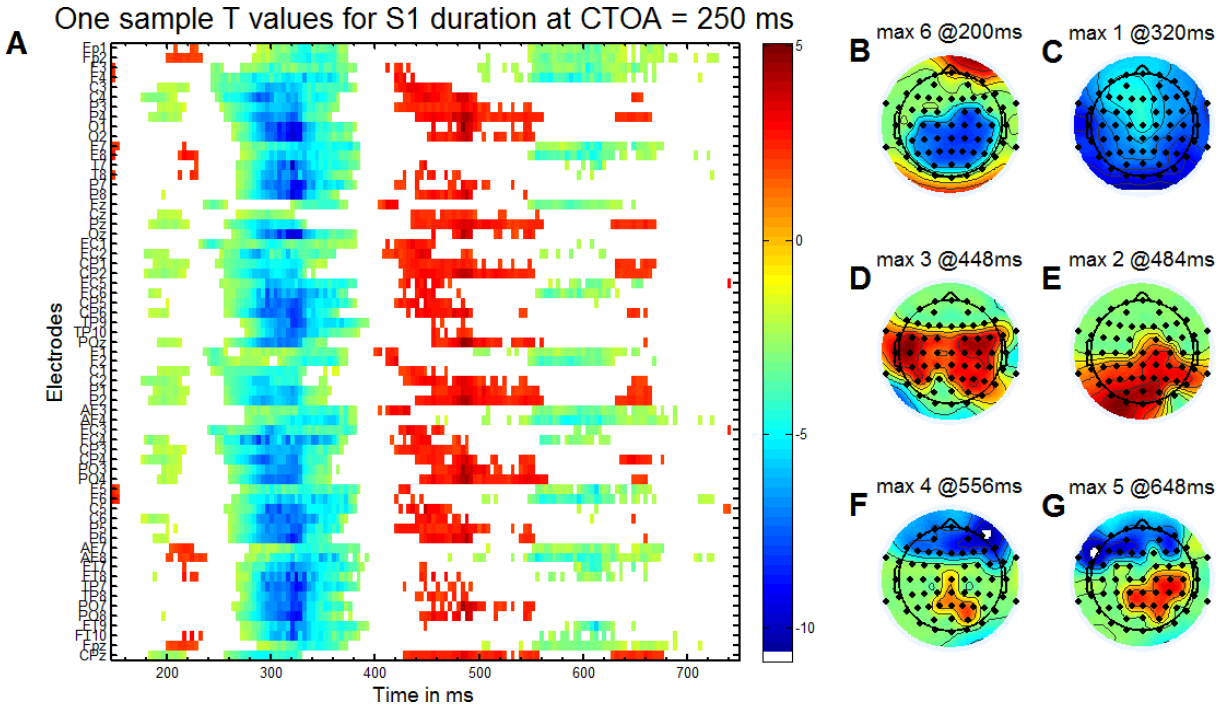


Figure 70 (A) Second level T-Test analysis for Duration of S1 as the condition on the 17 participants. Amplitude of T-values points in time per each channel at every participant having Condition as a Categorical Regressors for NSG condition after LIMO computation ((B-G) in the range of time from 148 to 748 ms). On the right the maximum is positive at (D) 484 ms.

In a third analysis a linear regression was applied on the 17 participants and 20 maximum R2 were averaged for both regressors. The individual explanation of the variance (R2) of this analysis is for short CTOA (TSG and NSG conditions). Therefore these four conditions were considered as the Categorical variables to run the linear regression. In addition, the Current Duration and the relative change of Duration were included as the Continuous Regressors.

Figure 71 shows the Second level T-Test analysis for Current Duration of S1 in the 17 participants. Amplitude of T-values points in time per each channel at every participant having Conditions NSG and TSG as the Categorical Regressors in the first level of linear modelling computations in LIMO (in the range of time from 148 to 748 ms). T-values results showed ERP waves around the MMN (negative frontal maximum at 200 ms) and the maximum at P300 (negative temporo-parietal maximum at 320 ms). In our analyses, stimuli duration evoke negative T-values MMN and P300, and the positive maximum is going from frontal 396 ms to 428 ms up to the right temporo-parietal 488 ms (see *Figure 71*.D-F), where RON waves should be. Therefore, our results are consistent in MMN with Pakarinen's results, and extend then for P300 and a RON. Possibly the managing of frequency does not show the pattern of RON in the ERP results.

The strongest T-values are still at 320 ms (*Figure 71*.C), are not as frontal as showed previously and also are more left lateralized. Therefore, the major changes are at the less frontal scalp predictions for Current Duration of S1.

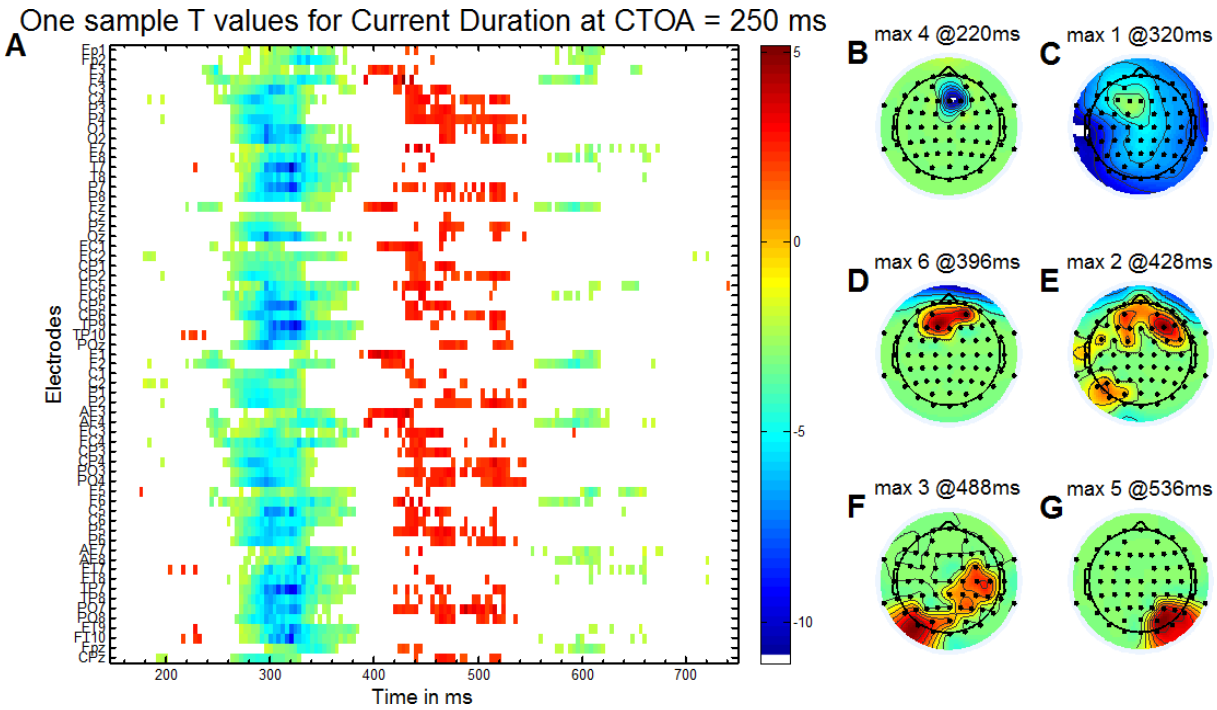


Figure 71 (A) Second level T-Test analysis for Current Duration of S1 in the 17 participants. Amplitude of T-values points in time per each channel at every participant having Condition as a Categorical Regressors for NSG condition after LIMO computation ((B-G) in the range of time from 148 to 748 ms). On the right the maximum is positive at (E) 428 ms.

Figure 72 shows the Second level T-Test analysis for the relative change of Duration of S1 in the 17 participants; this is the previous Duration minus the current Duration of S1. Amplitude of T-values points in time per each channel at every participant having Condition as a Categorical Regressors for NSG condition after LIMO computation (in the range of time from 148 to 748 ms). Now the strongest T-values are in a right frontal to left parietal scalp dipole at 220 ms (*Figure 72*.B). Also the second strongest T-values are in the right frontal and left parietal electrodes at 596 ms (= 346 ms for S2, *Figure 72*.G). The relative change of Duration is more in the MMN of S1 and the P300 of S2 for short CTOA.

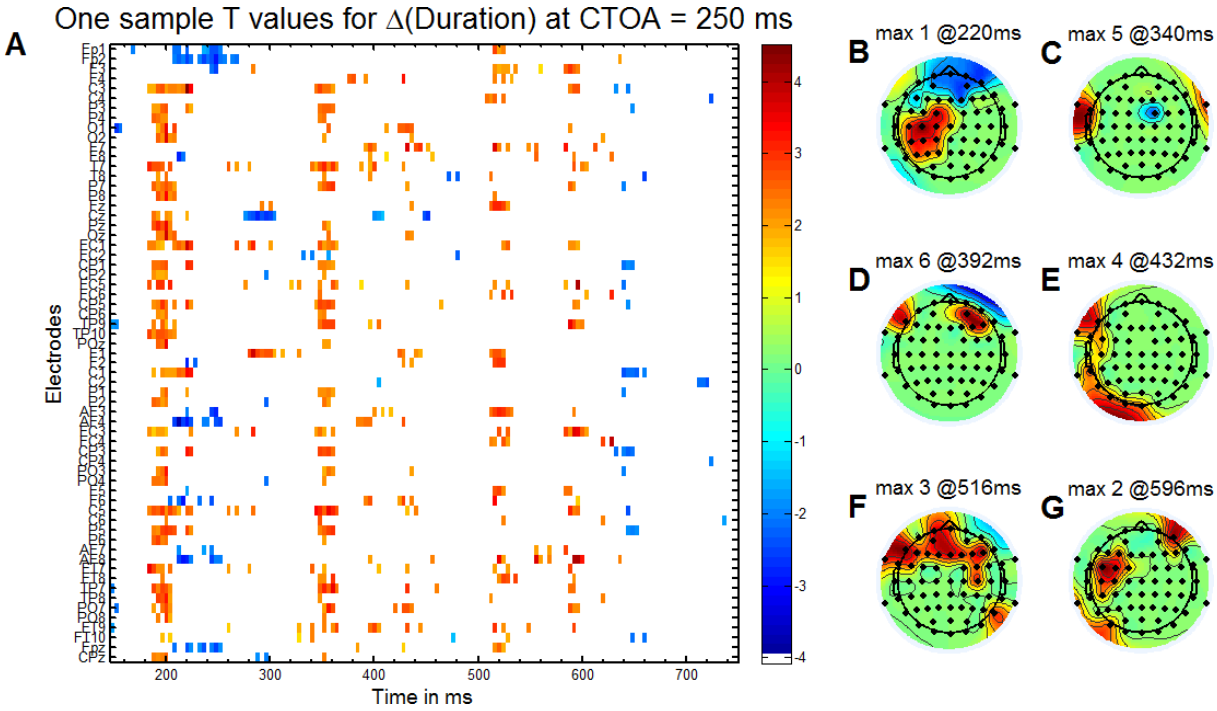


Figure 72 (A) Second level T-Test analysis for relative change of Duration of S1 in the 17 participants. Amplitude of T-values points in time per each channel at every participant

having Condition as a Categorical Regressors for NSG condition after LIMO computation ((B-G) in the range of time from 148 to 748 ms). On the right the maximum is positive at (B) 220 ms.

5.3.6 ERPs of long CTOA conditions in all the participants

Figure 73 shows the grand average ERP waveforms at 9 representative electrodes in the 17 control participants. The long CTOA conditions were considered to produce this average: Tone and after a Long time (500 ms) followed by the Goal number (TLG, in black), Novel and after a Long time (500 ms) followed by the Goal number (NLG, in red). The ERP difference NLG - TLG is shown in dotted lines in red, and the results of this difference showed that TLG is greater in frontal channels for N200 and P300 of the Novel stimulus and N200 of the second stimulus.

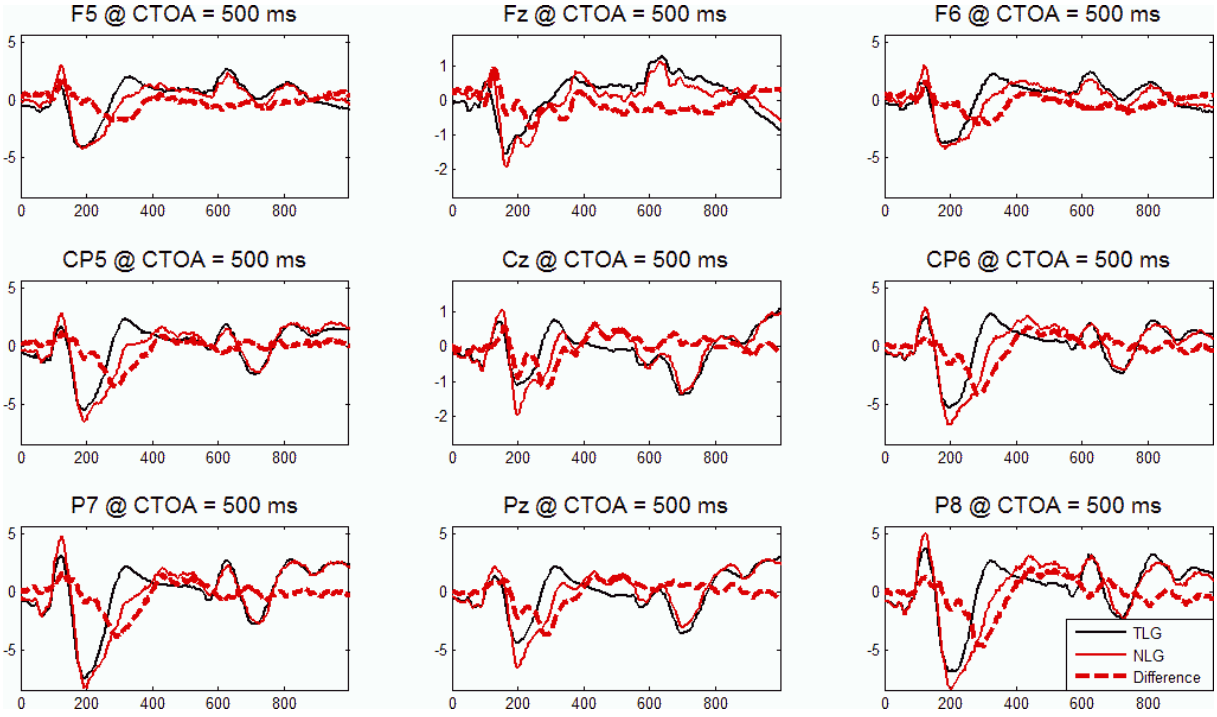


Figure 73 Grand average ERP waveforms at 9 representative electrodes in 17 control participants in the Tone and after a Long time (500 ms) followed by the Goal number (TLG, in black), Novel and after a Long time (500 ms) followed by the Goal number (NLG, in

red). The ERP difference NLG - TLG is shown in dotted lines in red. Note that TLG is greater in frontal channels for N200 and P300 of the Novel stimulus and N200 of the second stimulus.

5.3.7 Stimulus properties analysis in R2 in short CTOA in all the participants

The fourth analysis included the long CTOA conditions (TLG and NLG) in every epoched EEG dataset per each participant. The 38 properties were run as the Continuous Regressor in LIMO to determine which were the most significant predictors in this double CTOA switching task. Single subject results suggested that frequency and duration were the strongest predictors of the percentage of variance (R2). The second property (duration) was the strongest significant sound property when added as a regressor.

The individual R2 of this first analysis is for long CTOA (TLG and NLG conditions). After the 38 properties were run with the stimulus properties, single subject results suggested that the second property (duration) seems to be more significant when added as a regressor (see *Figure 74*). The strongest regressor was the relative change of ISI across most of the participants:

- Stimulus property 34 (relative change of ISI), in 6 participants shows more than 50% of the additional explanation of the variance R2
- Sound properties 1 (frequency) and 2 (duration) showed respectively, in 3 and 4 participants more than 50% of the additional explanation of the variance R2. This means that ISI changes were spread in more participants than the sound properties at the long CTOA of 500 ms.

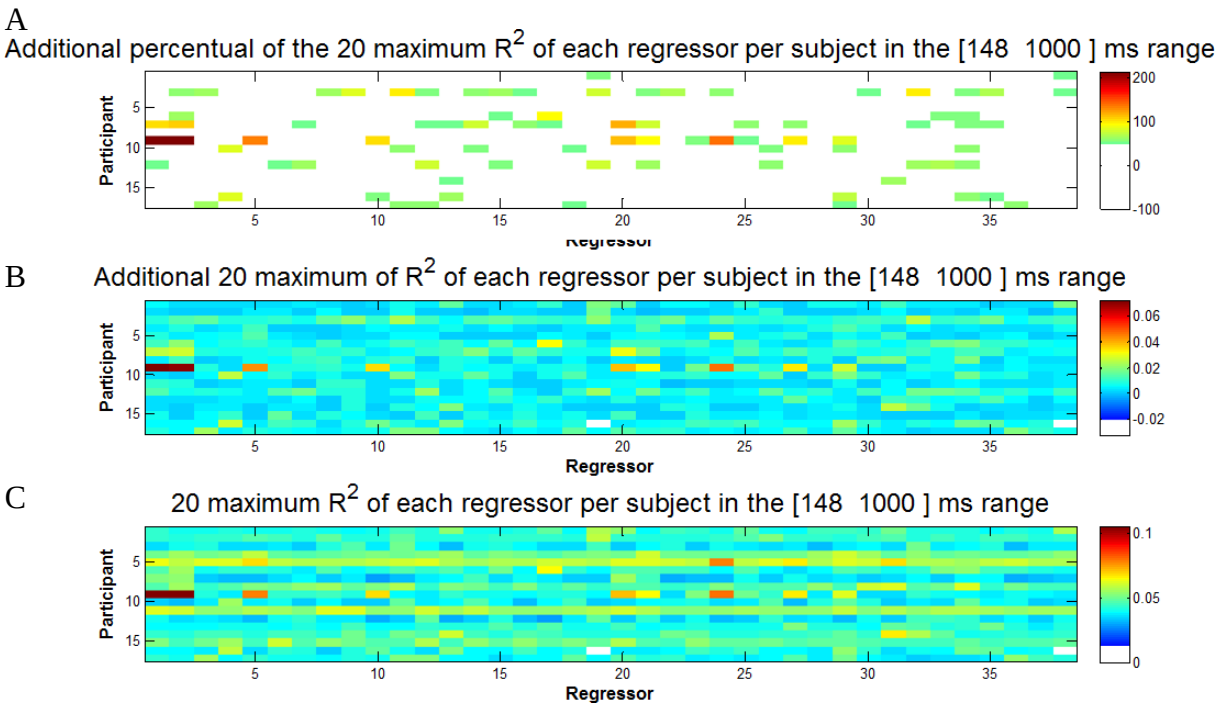


Figure 74 Averaging of the 10 maximum R2 points per each Property (see Table 3) as a Regressor added to the conditions for TLG and NLG conditions after LIMO computation (in the range of time from 148 to 748 ms). Amplitude scale is in colours and Regressors are in the horizontal axis and Participants in the vertical axis. A) Additional percentage of variance explained by each Regressor. B) Additional variance explained by the Regressor. C) Variance explained by the Regressor and Conditions.

5.3.8 Second level analysis in long CTOA

Figure 75 shows the Second level T-Test analysis for TLG condition in the 17 participants. Amplitude of T-values are given in colour at each point in time per each channel in the 17 participants. In the first level, the Conditions TLG and NLG were used as the Categorical Regressors for LIMO computation (in the range of time from 148 to 998 ms). On the right, the maxima are shown. The first negative maximum is at 152 ms (*Figure 75*.B) and the maximum is negative at 224 ms (*Figure 75*.C) going from the frontal to the temporo-parietal-occipital electrodes, respectively. This is consistent with the propagation of the waves for standard stimulus in perceptual ERP (*e.g.* Joosa, Gillesa, Van de Heyninga, De Ridderd, & Vannestea, 2014). There are also positive maximum at 332 ms (*Figure 75*.C), 364 ms

(*Figure 75*.D) and 392 ms *Figure 75*.F) with bilateral, non-central, and non-central strongly bilateral distributions, respectively, biased to the left. This result is consistent with the exogenous bilateral control of attention (Corbetta & Shulman, 2002) and biased to the left for standard stimulus (Corbetta et al., 2008). Overall, all results for TLG condition are stronger in the times given for the Tone in S1.

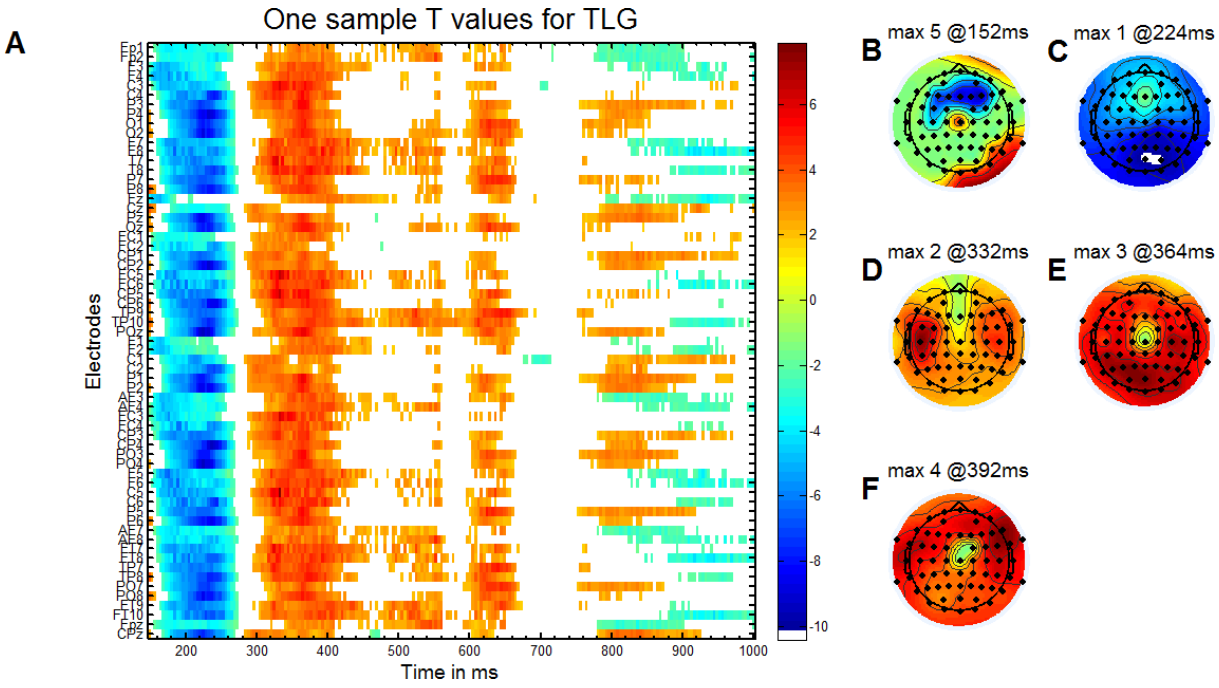


Figure 75 (A) Second level T-Test analysis for TLG condition on the 17 participants. Amplitude of T-values points in time per each channel at every participant having TLG and NLG conditions as the Categorical Regressors ((B-F) in the range of time from 148 to 998 ms). On the right (C) shows that the maximum value is negative at 224 ms around MMN range. Note that P300 is significant evoked in 3 maxima T-values.

Figure 76 shows the Second level T-Test analysis for NLG condition on the 17 participants. Amplitude of T-values are given by colour at each point defined in time per each channel in the 17 participant's group. In the first level Conditions TLG and NLG were used as the Categorical Regressors for LIMO computation (in the range of time from 152 to 224 ms). Non-frontal but left lateralized electrodes showed a negative maximum is at 196 ms (*Figure*

76.B), with the other 5 maxima at more than 500 ms. P300 for the Goal S2 showed significant frontal scalp activation around 876 ms (= 376 ms for S2, *Figure 76*.F) and sliding from 824 ms (= 324 ms for S2, *Figure 76*.E) up to 976 ms (= 476 ms for S2, *Figure 76*.G). On the other hand, the P300 for the novel S1 did not show as strongly as the rest of the R2 measured along the range of time.

These results showed an important influence of the NLG at the alerting signals for S1 and in the processing of the Goal stimulus. In other words, the larger CTOA the more Goal-driven the effect for Novel events in S1. This is consistent with the current view of exogenous cues (Wright & Ward, 2008).

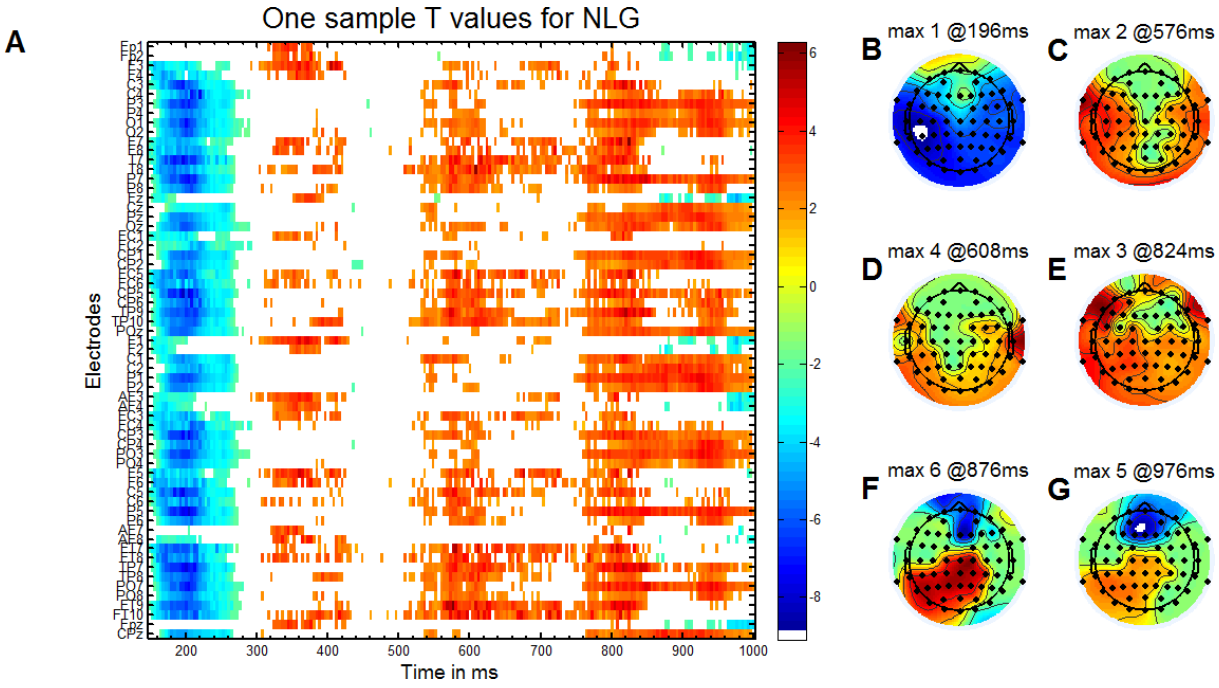


Figure 76 (A) Second level T-Test analysis for NLG condition on the 17 participants. Amplitude of T-values points in time per each channel at every participant having TLG and NLG conditions as the Categorical Regressors ((B-G) in the range of time from 148 to 998 ms). On the right (B) shows that the maximum value is negative at 196 ms around MMN range. Note that although P300 is significant evoked, it is not one of the 6 peaks.

Figure 77 shows the Second level T-Test analysis for Duration of S1 in the 17 participants. Amplitude of T-values are given by colour intensity points defined in time per each channel for the 17 participants In the first level Conditions TLG and NLG were used as the Categorical Regressors and Duration of S1 was used as the Continuous Regressors for LIMO computation (in the range of time from 152 to 224 ms). The maxima points are after Goal stimulus, starting in the bilateral fronto-parietal scalp network at 872 ms (= 372 ms for S2, *Figure 77*.D), going to the maximum in the left temporo-parietal electrodes at 900 ms (= 400 ms for S2), and finishing at 932 ms (= 432 ms for S2, *Figure 77*.F). Later, it continues to the central electrodes at 980 ms (*Figure 77*.G). The other relevant maximum is a possible dipole between positive right frontal and left parietal electrodes at 252 ms (*Figure 77*.B). On the other hand, the P300 for the novel S1 did not show as strongly as the rest of the R2 measured along the range of time.

These results showed an important influence of the Duration in S1 in the processing of the Goal stimulus. In other words, the larger CTOA the more Goal-driven the effect for standard Tones. This is consistent with current view of exogenous cues (Wright & Ward, 2008). However, some stimulus-driven properties are still in the dipole observed at around 252 ms in S1 (*Figure 77*.B).

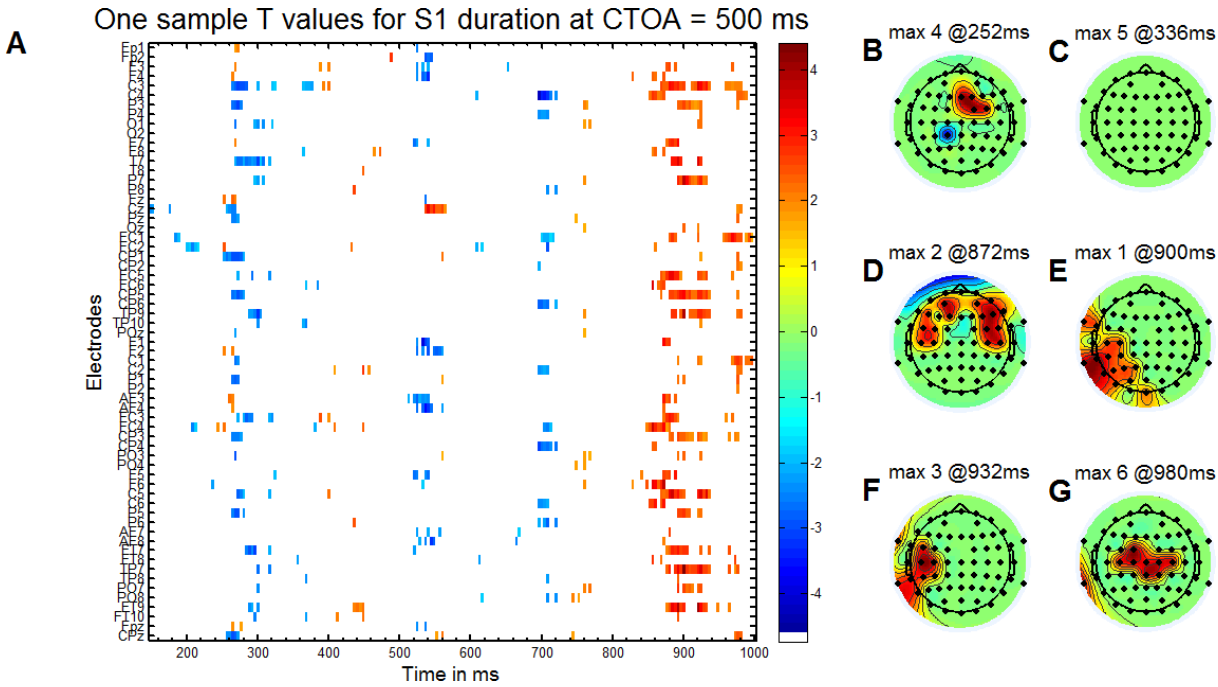


Figure 77 (A) Second level T-Test analysis for Duration of S1 on the 17 participants. Amplitude of T-values points in time per each channel at every participant having TLG and NLG conditions as the Categorical Regressors ((B-G) in the range of time from 148 to 998 ms). On the right B shows that the maximum value is negative at 196 ms around MMN range. Note that although P300 is significant evoked, it is not one of the 6 peaks.

The analysis of the results of the experiment showed that the properties parametrically manipulated (frequency and duration) had significantly more relevant R2 than the other 36 properties when CTOA = 250 ms. In this way, at CTOA = 500ms, the R2 of the other properties is similar to the analysed level.

5.4 Discussion

In summary the sound properties (duration and frequency) were most important at short CTOA (supporting H1, H2 and H3) being frontally at the scalp (not supporting H5) and the local change of timing presentation (relative change of ISI) was important at long CTOA

(supporting partially H4 due to selective long CTOA).

The first interpretation of these results is that the manipulated/parametric properties are directly linked to exogenous events such as it happens in the Posner paradigm (Wright & Ward, 2008 see Figure 78, upper and middle text) and the bilateral activation of the stimulus-driven system proposed Corbetta and collaborators (Corbetta & Shulman, 2002). The bilateral distribution of TSG and TLG conditions supports this interpretation and gives a new interpretation with the sound properties importance for short CTOA and timing presentation for long CTOA (see Figure 78, lower highlighted text). This highlighted the contribution of the use of information theory to design the experiment, not only in the optimal number of trials, but also in the parametric study and the use of two CTOAs for the analysis. In this manner to extend the interpretation, it is suggested another experiment with the manipulation of endogenous events with these properties, and see if these are the result only of time or are related to the type of event. The experiment proposed to this validation would be an alarm to indicate where the participant should find/ hear the sound. Therefore, having this interpretation and the activation of exogenous cues (McCormick, 1997), the hypothesis would be that the effect should be the inverse, where the sound properties of the stimuli would be important when CTOA = 500 ms and local probability effects would be important at CTOA = 250 ms

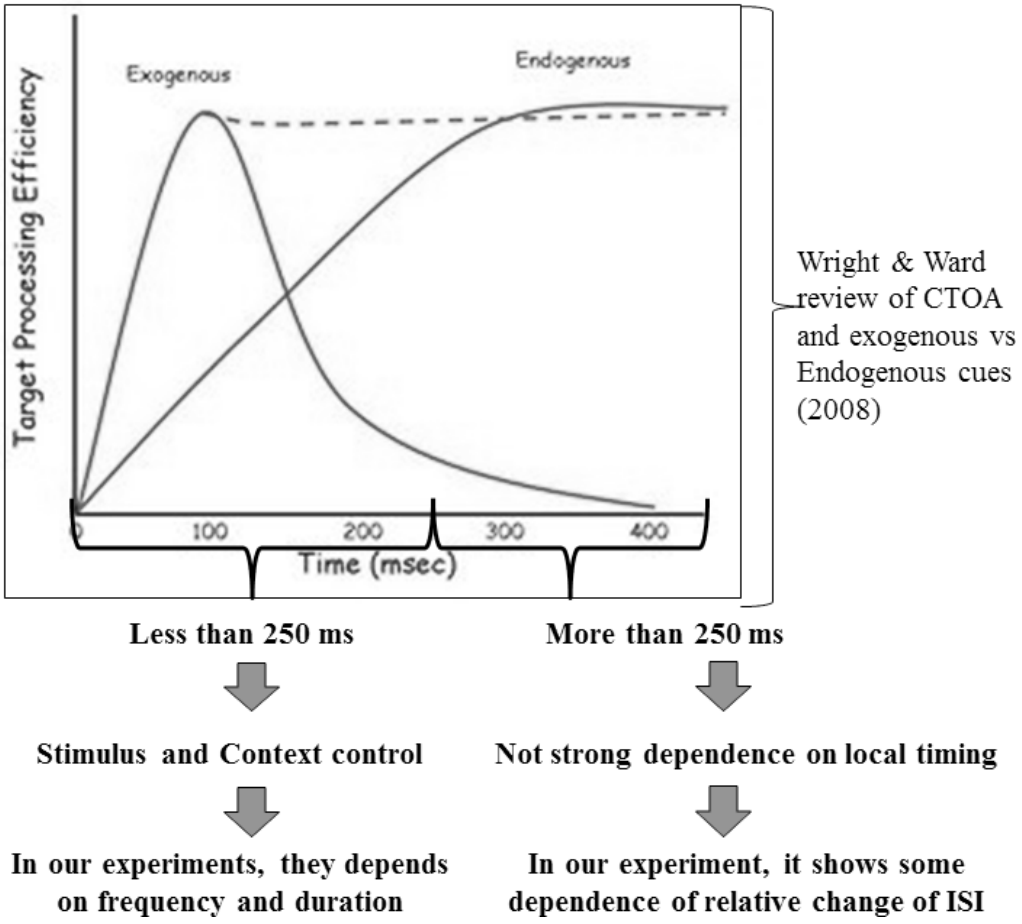


Figure 78 Stimulus and Context control interpretation for the parametric experiment with changes in CTOA. The rectangle shows the suggested CTOA and exogenous and endogenous effects in attention tasks (Wright and Ward, 1998). Outside the rectangle is what we added with our analysis along the Chapters 2, 4 and 5.

The second interpretation of the results is that they are consistent not only with the frontal P3a waves reported for novel stimulus (*e.g.* see P300 review in Polich, 2007) but also with the more frontal contextual control on the executive model of Koechlin (Koechlin et al. 2003). Thus, the bilateral evidence of significant differences in the case of the TSG condition, is going to the frontal scalp side in the case of the NSG condition. This result supports the findings and interpretation for context dependent analysis showed in the new events followed by the standard event reported in Chapter 2. Our results add to Koechlin's interpretation that

the temporal context is more important when the CTOA is larger for exogenous events (see properties analysis in *Figure 74* in section 5.3.4). It is also in relative change of Duration, that this Regressor makes negative frontal on the scalp at 220 ms and affecting later in importance to 596 ms (= 246 ms for S2). This result showed a more frontal scalp effect in context dependent analysis.

In the third interpretation of the present study a longer ISI was introduced to disambiguate alerting stimulus and the goal stimulus effects. Previous research has identified clear effects of ISI on the P3a response in particular at parietal electrode positions (Miltner, Johnson, & Braun, 1991; Polich, 1990b; Polich & Bondurant, 1997). Therefore on the one hand, novel P3a amplitude must show significant variation over time but with strong dependence on the inter-trial intervals. As predicted by Gonsalvez & Polich (2002) the larger the inter-trial intervals (ITI), the larger the amplitude of P3a peak from 1 [s] to 16 [s] between interstimuli for parietal electrodes, although this effect was only marginally reliable for auditory and visual stimuli over midline electrode positions. (Gonsalvez & Polich, 2002). Our result are at times less than 1 s, then the ISI effect is reliable at 500 ms and not at 250 ms. The remaining question is: whether having 2 variations more for ITI influences in the attenuation of the ISI effect.

A fourth interpretation of these results is that the duration properties even when there is a switching task in CTOA. The P3a and RON appeared for NSG condition, the longer the duration the more attenuation for MMN, P3a and RON of the stimuli for TSG and NSG, at 484 ms in NSG condition, the positive wave to the parietal central electrodes.

On the other hand, Yago and colleagues found right frontal scalp activation for MMN and suggested a complex network involved in frequency change (Yago, Escera, Alho, & Giard,

2001), this is similar for the Corbetta's model of stimulus-driven network at orienting of attention (Corbetta et al., 2008). Pakarinen and colleagues aimed to study MMN using only non-standard stimulus, their experiment used eight frequency tones at different intensities and durations with an intertrial interval of 500 ms. Participants were asked to watch a subtitled movie ignoring the sounds. MMN was observed stronger liked to duration than to frequency (Pakarinen, Huotilainen, & Näätänen, 2010). Therefore, a fifth interpretation of the present results is that duration appeared with MMN in the short CTOA (*Figure 70*) but not at long CTOA (*Figure 77*). In the light of these results, MMN was more related with short CTOA at 250 ms, the range time of Wright & Ward CTOA for endogeneous stimulus target processing. Therefore, orienting of attention is suggested for this short CTOA.

In the previous study (Chapter 2) an alerting stimulus was used prior to the goal task and the ERPs in that condition were compared to the responses evoked by a novel stimulus that replaced the alerting stimulus. The purpose of this design was to explore the effects of time and properties in the process of distraction on the goal task performance when an orienting response was generated. An important element of the previous analyses (in Chapters 2 and 3) was to explore the effects of stimulus properties, global probability, and local probability. A specific problem with the previous design (Chapter 2) was the overlap of the ERP response to the alerting stimulus and the goal stimulus; here that overlap was studied through both CTOAs (250 ms and 500 ms).

6 DISCUSSION: FINDINGS, LIMITATIONS, AND FUTURE DIRECTIONS.

General Discussion

The original aim of this research was to use ERP markers such as P300 (Polich, 2007) to better understand the relationship between the stimulus driven attention network and the goal driven network as described by Corbetta and colleagues (Corbetta & Shulman, 2002, Corbetta et al, 2008). An attempt was made to improve the sensitivity of the ERP analyses by exploring the effects of: variations in stimulus properties (*e.g.* temporal probability, frequency, duration, amplitude), information of the train of stimulus, and context dependent stimulus on patterns of neural signals detectable at the scalp, using bootstrap correlations and linear modelling. An important alternative, historical hypothesis is that the goal-driven network initiates orienting prior to the stimulus-driven network and that this is consistent with the view that the stimulus-driven network as better considered as a system involved in context updating (Donchin, 1981; Polich, 2007). On the basis of these studies, further ERP studies were carried out in an attempt to optimise the design experiments for understanding exogeneous stimulis in orienting of attention and future combined EEG and fMRI studies.

Experiments and theoretical parts analysed.

Throughout the thesis exogenous stimuli were explored (standard tones T, and new stimuli N) for a number decision task (Goal number, G). The general aim was to understand the phenomenon that occurs in attention distraction in humans. In Chapter 2 a number parity decision task EEG experiment with 4 conditions Tone Goal (TG), Novel Goal (NG), Novel only Tone (NT), Tone simultaneous Novel and Goal (TNG) was used in controls and schizophrenia patients (*Figure 26*.A). Results revealed that stimulus properties are correlated with P300 and other ERP deflections. In Chapter 3, the opportunity was taken during the technical development of combined EEG and fMRI to run a number parity decision task with

4 conditions: Goal number (G), Zero (Z), simultaneous Novel Goal (NG) and Novel (N) (*Figure 26*.B). Results revealed activation in the right hemisphere when 'distracted' participants were analysed. In Chapter 4, a pilot experiment (*Figure 26*.C), results revealed that environmental sounds were better for evoking a P3a response. In addition, a study of information theory experiments was performed based on the experimental auditory results (*Figure 26*.D). Here, it was believed that this simulation saved several experiments to get the results. Results revealed a change in the entropy of the stimuli sequence produced around the Continuous Target Onset Asynchrony (CTOA) at 300 ms. Finally, in Chapter 5, an EEG study was run with 4 conditions Tone Short Goal (TSG), Tone Short Novel (TSN), Tone Long Goal (TLG) and Novel Long Goal (NLG) (*Figure 26*.E). The results confirmed frequency and duration as the reliable predictors for P300 response.

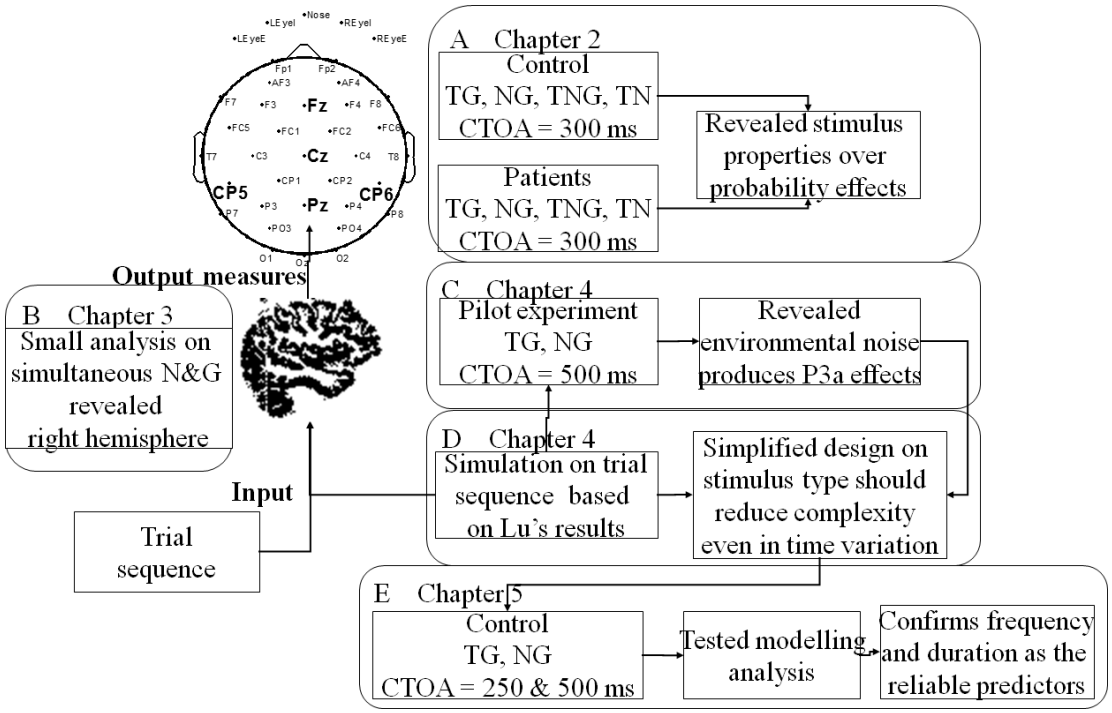


Figure 79 Experimental designs employed throughout this dissertation.

Stimulus properties and Local Probability

Currently, Local Probability is believed to be the determinant for the generation of neuronal activity when a new stimulus appears (*e.g.* reviewed in Polich, 2007; Gonsalves & Polich,

2002), though in recent years some reports in multimodal experiments including visual stimuli suggest that the temporal properties of auditory stimuli are significant in the modulation of the reaction times (Hughes et al., 2007; Parmentier et al.,2010). In Chapter 2, an existing experiment with 4 conditions was explored in control participants and schizophrenic patients. As a result, these four conditions altered the typical response of the correlation of the inter-stimuli with the P300 wave in the oddball experiment. For the Novel preceding the Goal (NG) condition, in the control participants a significant correlation of the P300 wave and sound properties of the stimuli was found with a right lateralisation response associated with sounds presented on the right side. The sound properties pointed to over long term average spectrum and entropy (LTAS and Entropy) with the previous Goal Stimulus (S2) was observed for both left and right sounds (*Figure 80*.A). On the other hand, in schizophrenic patients it was found that there were negative correlations of the P300 deflection with duration of the events and positive correlations with measures of long term average spectrum and entropy (LTAS and entropy *Figure 80*C). This experiment therefore extends the recent findings of multimodal experiments (Hughes et al., 2007; Parmentier et al., 2010) to auditory stimuli unimodal mode based on the properties of stimuli. However, given the number of conditions and associated multiple variables of the sounds in the experiment, this resulted in a complicated analysis. On the basis of these findings and simulations of the information of the stimuli used in Chapter 4 a simpler parametric experiment was eventually designed as described in Chapter 5. In Chapter 5, temporal variation in the NG and TG conditions were explored, using a short CTOA (250 ms) and a long CTOA (500 ms). Again, it was found that the properties of stimuli in selective attention tasks are important, in particular the duration of the Novel stimuli and its effect on P300 amplitude. In addition, the ERP answer to the Novel stimulus was frontally biased in the short CTOA condition, having the stimulus duration as the regressor for the Novel stimulus, consistent with the prefrontal control of attention (see *Figure 80*.B).

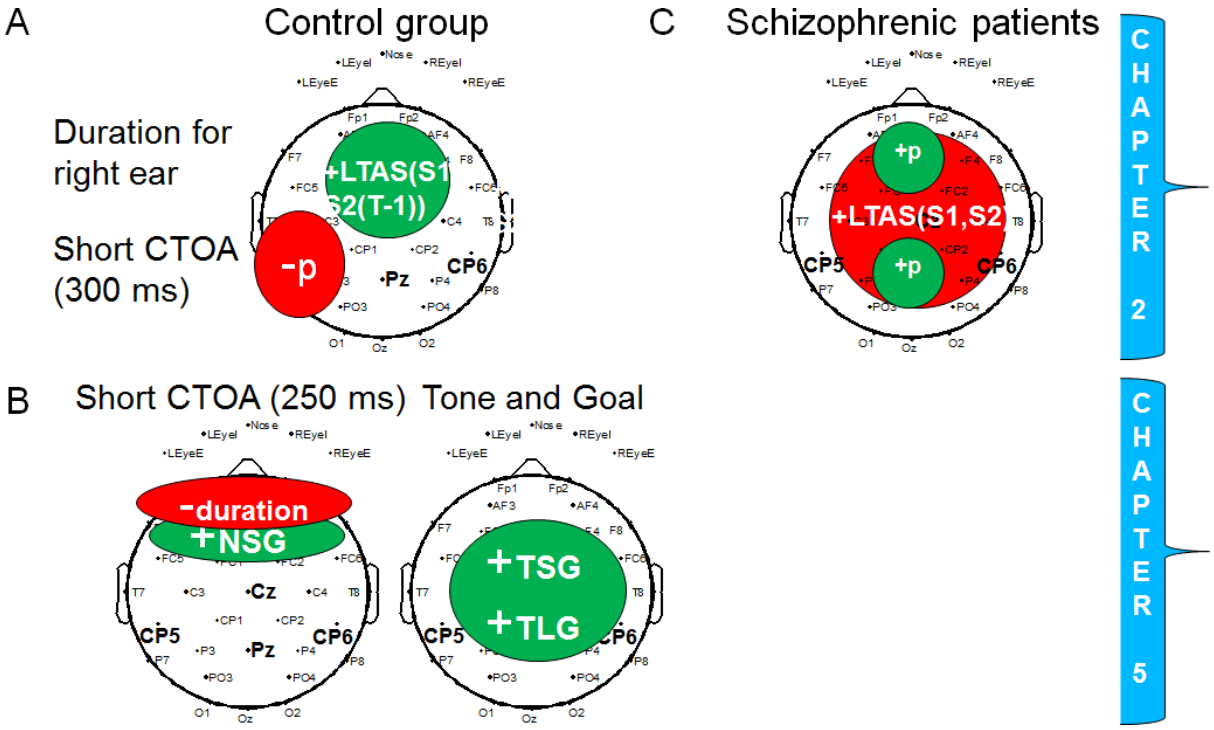


Figure 80 Comparison of experimental results in Chapter 2 and 5. Local stimulus probability was shown localized to a few electrodes for the control (based on any previous novel NG, TNG or TN) and schizophrenic group (with previous NG), single trial results pointed to LTAS predominantly in schizophrenic patients. On the other hand when the different CTOA times in the parametric design were analysed, from Novel Short Goal (NSG) was found for P300 and negative duration. Small but significant amplitude changes were found for Tone Short Goal (TSG) and Tone Long Goal (TLG) condition.

Based on the previous experimental comparisons of stimulus properties, the different CTOA could be used to test sound properties in a new parametric experiment (*e.g.* similar to the experiment in Control and Schizophrenic patients as discussed in Chapter 2). This could enable the determination of whether different exogenous and endogenous stimuli may produce clearer differences in NG condition results between Controls and Schizophrenic patients. Therefore, the research questions can point to LTAS, duration or frequency interactions with endogenous and exogenous cues and/or point to different endogenous and

exogenous stimulus properties in the CTOA dimension. In this way the general hypothesis would be whether the endogenous experiment produces complementary explanations of the exogenous experiments. The specific hypotheses are:

H1: CTOA < 250 ms there is no strong dependence of local timing in CTOA

H2: CTOA > 250 ms there is stimulus and context control of sound properties such as frequency and duration or possible LTAS.

Novel MisMatch Negativity (MMN) findings in schizophrenic patients

With regard to the scientific literature, MMN is frontally attenuated in the scalp of schizophrenic patients (Näätänen & Kähkönen, 2009). Further, the results of neuroimaging and ERP results indicate that when a task has little difficulty, temporal processing in patients with schizophrenia is not affected (Davalos, Tregellas & Rojas, 2011). For schizophrenic patients, in the study reported in Chapter 2, it was found that the MMN wave is modulated differently depending on how much time had elapsed since a novel sound had occurred in the stimulus sequence before the current warning signal (*i.e.* TG.NG, TNG.TG and TN.TG) and this finding is consistent with the impairment in context processing over episodic events in schizophrenic patients (Chambon et al., 2008) in the light of the role of memory in the hierarchical model of prefrontal control of Koechlin and colleagues (2003, 2007), although the present results were based on scalp recorded signals. In other words, the MMN evoked by the next standard tone cue was larger as the duration since the previous novel sound got smaller. This suggests that the individuals with Schizophrenia are affected by the novelty of the environmental sounds to a greater extent than the controls at a very early stage of processing, or that maintenance of the template for the frequent Tone cue is impaired.

This finding of the contextual MMN in terms of brain activity is consistent with the auditory fMRI experiment discussed in chapter 3, where the number decision paradigm produced different brain activations, some of them with different Brodmann Areas and other similar

brain activations in different hemispheres depending on the contrast and its direction. In this way, chapter 3 suggested that the MMN would have a different ERP deflection from the N200 in EEG or fMRI brain region in ACC depending on the analysis of all participants or only the 'distracted' participants. Therefore the MMN would process events in time dependence between two consecutive stimuli and on the behavioural distraction as well.

The question is therefore whether novel stimuli activate different regions of the brain in schizophrenic patients or whether the signals that were observed are the result of a different pattern of activation in the same regions of the brain. This question might be addressed through dynamic causal modelling (DCM) to re-analyse the experiment discussed in Chapter 2 for MMN and look more closely at the effects differences in the properties of the stimuli and Local Probability for TN and TNG conditions.

According to the results of Court and colleagues, from a post-mortem study of schizophrenics and of Lewy bodies in dementia, patients showing a reduced activity of TRN neurons is the result of reduced cholinergic binding (Court et al., 1999). Also, there is known the P3a reduction by haloperidol (Kähkönen et al., 2002) see Figure 2 (Chapter 1), adding the reduction of P300 response was reduced under ketamine (antagonist of NMDA receptors) that may be prevented by haloperidol (Oranje et al., 2009). Therefore, the DCM analysis and our mutual information findings suggest a useful experiment would involve correlating blood sample results and EEG or fMRI. The aim would be to determine whether psychosis was induced by: (1) NMDA antagonists (*e.g.*, PCP) blocking NMDA receptors in the Cortex, TRN, and Thalamus producing a reduction in TRN GABA release, which results in an increase in the activity of cortex-Thalamus and Thalamus-cortex a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) excitatory synapses; or (2) deficits of TRN Gamma Amino Butyric Acid (GABA)ergic deficits in TRN GABAergic neurons inducing a similar

increase in the activity of cortex-Thalamus and Thalamus-cortex connections, which is mediated by both AMPA and NMDA synapses. One needs to note that this experiment should show different result because NMDA relates to cortical and subcortical impairment whilst GABA is a subcortical impairment that would allow having different measures under an oddball task in EEG or fMRI studies.

The results of DCM would possibly be correlated with Court's findings and results in the sources of the TRN neurons as the result of the reduced cholinergic binding (Court et al., 1999) and the Ferrarelli's model of NMDA and AMPA. Ferrarelli interpreted that NMDA and AMPA are managed by different receptor in the layers going from the Thalamus, TRN and layers VI, V and IV of the brain cortex (Ferrarelli et. al., 2010). We can test DCM results using an experimental model based on temporal sequence analysis to indicate the different possibilities of NMDA and AMPA receptors that could involve different activation of the standard stimulus (N200) from the novel stimulus (MMN) in an auditory exogenous experiment. Thus, the ratio of the timing of events and LTAS's measures may bring new approaches to the modelling of temporal processing in orienting attention in schizophrenia. The overall reflection suggests that cognitive impairment changes stimulus processing in the schizophrenic patients (LTAS and entropy processing) can be evaluated using other CTOAs (*e.g.* 500 ms).

At this point the re-analysis of schizophrenia and control EEG data may consider the analysis of amplitude as loudness effects in the N100 and P200 measure and find the different modulation of the four conditions (where the TN condition is a NoGo task) with the dependence of the loudness mostly studied for Goal tasks formely studied in anxiety (e.g. Senkowski, Linden, Zubrägel, Bär, & Gallinat, 2003) and later in schizophrenia (e.g. Park, Lim, Kim, & Bae, 2009).

Differences in the activation of prefrontal areas when Novel stimuli precede the warning signal.

With regard to prefrontal attention control, it has recently been proposed that preceding stimuli produce different prefrontal activations depending on the experimental task, having the spatially more prefrontal activation the more complex the control of attention made from stimulus, contextual episodic or branching (Koechlin et al. 2003, Koechlin & Summerfield, 2007). In Chapter 3, a subgroup of participants who showed a 'distracting' behavioral response in terms of reaction times and, broadly, fMRI results showed brain responses in both hemispheres. Thus, in this 'distracted' subgroup (n = 6) the brain regions are activated differently when the previous stimulus has the novel stimulus of a different configuration. This result, considered in the light of the different experimental results in the novel conditions in controls and schizophrenic patients discussed in Chapter 2, leads one to consider the possibility of studying the brain regions activated by a previous distraction based on the properties of the stimuli in the sequence of trials based on the previous conditions of the experiment. Therefore, the analysis of EEG and/or fMRI as discussed in Chapter 3 may be extended to find the relevant stimulus properties, which may be different to those in mentioned in Chapters 2 and 5, according to the influence of the scanner background noise found in the pilot study in discussed in Chapter 4. Finally, as one can see in *Figure 81*, these stimulus properties may be used as regressors in the fMRI analysis in order to find whether there is prefrontal control of orienting of attention (see highlighted arrow). A further matching with other literature results may either use better modelling or another type of experiment.

Scanner background noise (SBN) changes the frequency reference for the sound stimulus.

A pilot experiment was performed in Chapter 4 based on the results for environmental sound properties in the EEG experiment discussed in Chapter 2 and a lack of representative P3a for novel sounds in the 'distracted' subgroup in the simultaneous EEG/fMRI experiment discussed in Chapter 3. The pilot study explored the effect of scanner background noise (SBN) on responses evoked by environmental sounds to study different effects in distraction between Tone followed by the Goal (TG) and Novel followed by the Goal (NG) conditions. The experiment suggested that the SBN alters the background signal to a new frequency reference, where the environmental noise type would be similar to a standard noise and the white noise relative to the SBN is similar to an environmental noise. This result may be correlated with the fMRI experiment set out in Chapter 3, where no significant signal for P300 to novel stimuli (condition N) was found. Care must therefore be taken to ensure that the goal stimuli and novel stimuli are chosen so that they exist in a region of the temporal and frequency domains that is distinct from the SBN, moreover results suggested a different temporal and amplitude noise induced by the different stimulus in every condition. Thus, the effect of relative sound may be not only in the warning signal as discussed in Chapter 2 but also in the exogenous stimulus and the re-analysis set out in Chapter 3 must consider splitting 'environmental sound' and 'white noise' similar to that discussed in Chapter 2. This means, in the case of EEG signals, that the analysis may be with Linear Modelling or the combined single trial average and Bootstrap correlation using the measure of the sound properties of the stimulus (e.g. EEG experiment in Chapter 2) and the first level of the fMRI analysis may be constrained by the significant regressors of the EEG analysis (see *Figure 81*). The analysis may also be extended to understand the differences between different types of sounds, with the segregation between both types of sound (white and environmental sounds), as highlighted in the text after the measures of sound properties in the extended analysis shown in *Figure 81*. In addition to the above, the relative sound measure differences may support not only the analysis in the Transverse Temporal Gyrus found in chapter 3 but also of other

deep areas.

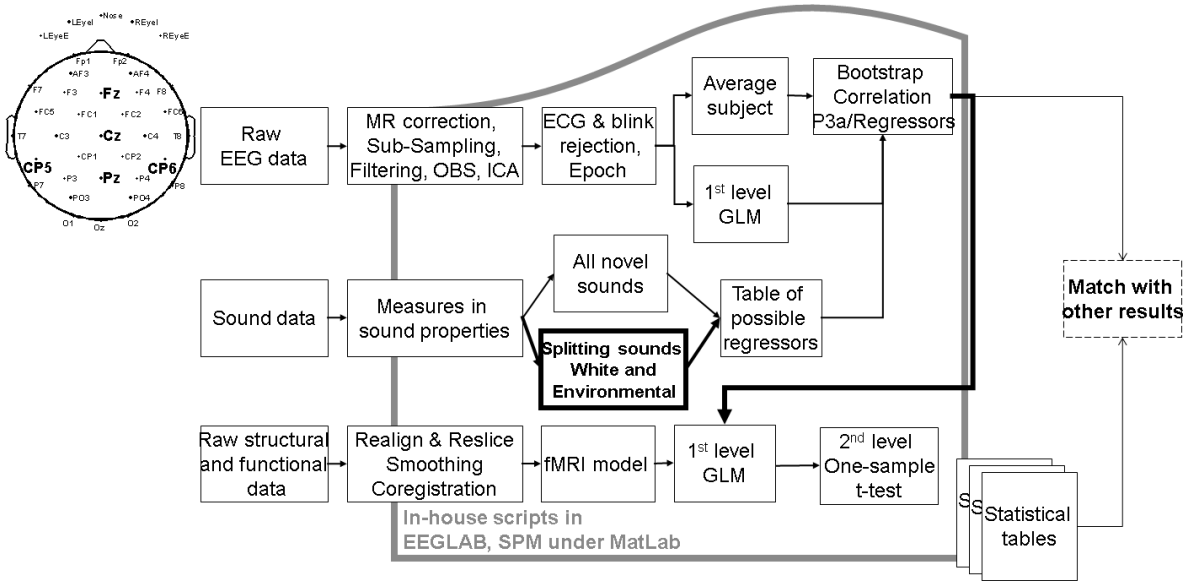


Figure 81 New analysis proposed to study the simultaneous EEG and fMRI to seek whether: stimulus properties may be used for both EEG and fMRI and moreover make and fMRI informed by EEG.

Using information theory to design stimuli and the time in the care of endogenous stimuli

Due to the different and correlated results in the experiments described in chapters 2, 3 and 4, a model was constructed on the basis of information theory. The results pointed to stable information content of stimulus information from more than 60 novel stimuli. Therefore, with more novel stimuli, a better study of the cortical processing could consider a minimum interference of the trial sequence. In this way, the EEG experiment was designed in Chapter 5 taking into consideration the temporal effect of the sounds presented and the frequency response of the noise in order to assess what effect local probability, the presentation time between stimuli (CTOA) or the intrinsic properties of the stimuli presented were more or less significant in driving the response to novel stimuli.

In Chapter 5, the results suggest that the frequency and duration of the current event and the previous event influence changes in electrical activity more significantly than CTOA (250 ms and 500 ms) or the local probability. Thus, these results reinforce the idea that the orienting of attention caused by exogenous stimulus is based on the properties of the stimuli.

On the basis of these findings:

First, adding a condition where the information of the sequence in the task makes a change in the curve of the change logarithmic information (a kind of entropy), as shown in the top part of *Figure 82*, where there are CTOAs in the time window from 300 to 400 ms with a different indentation in informational content (see between yellow lines).

Therefore, a new CTOA at 375 ms is proposed such that is in the indentation highlighted in yellow in the top part of *Figure 82* projected to the Wright and Ward picture review of CTOA in the middle part of *Figure 82*. This is introducing a CTOA in the transient between 300 and 400 ms (see between yellow lines). We introduce a new CTOA to understand better not only this new CTOA but also the changes across different information states studied here: CTOA (at 250 ms and at 500 ms in chapter 5).

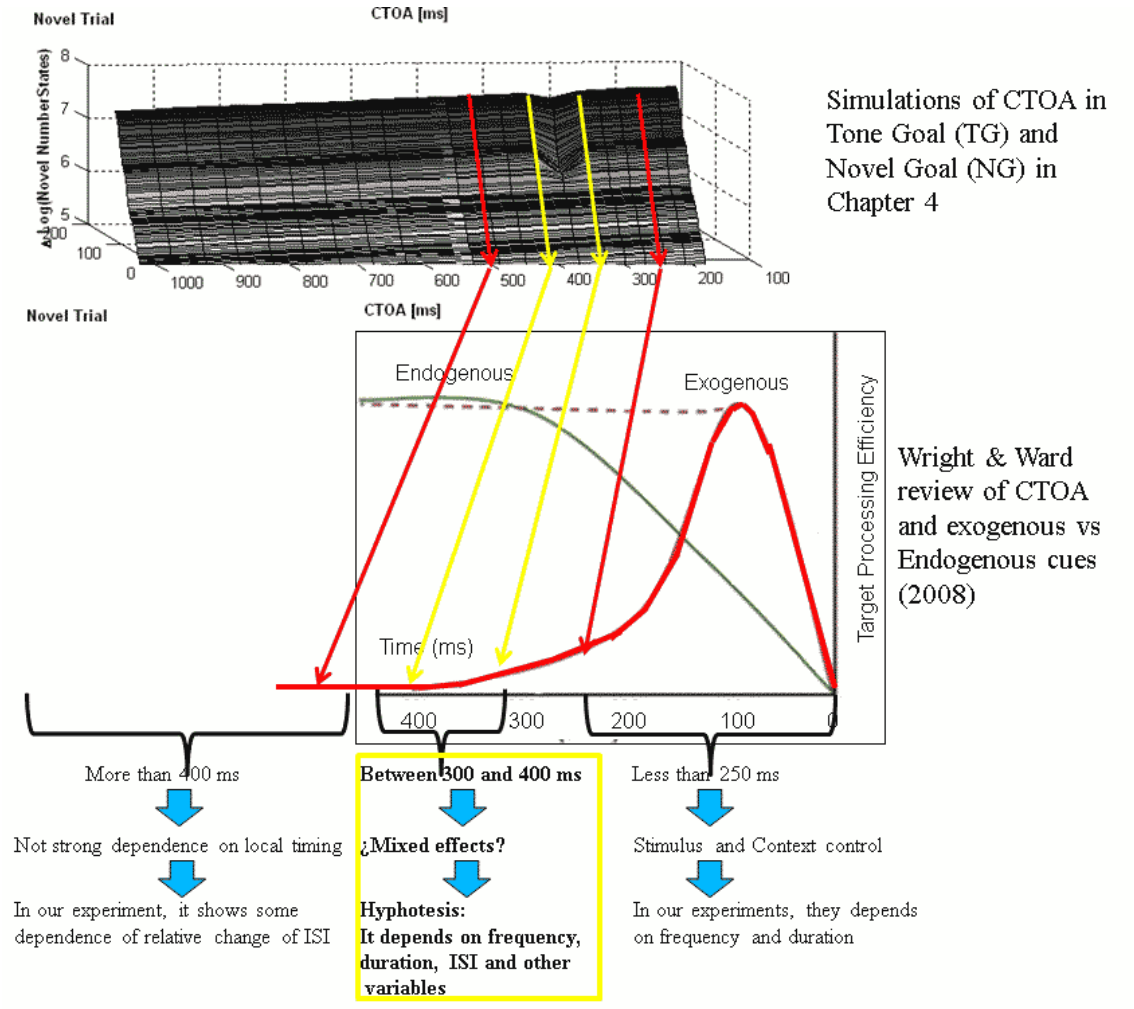


Figure 82 New experimental hypothesis to determine whether the stimulus properties are changing gradually at different CTOAs.

Finally, in this thesis it is proposed to carry out an experiment of endogenous stimuli to extend the present investigation. It is also proposed to continue with an analysis that considers the current event based on the previous event. In this way the experiment considers three CTOA (*e.g.* 250 ms, 375 ms and 500 ms) and endogenous and exogenous modalities.

In addition, from the conclusions it may be possible to re-analyze switching in the four conditions with CTOA around the 300 ms as was carried out in the experiment discussed in

Chapter 2 and help to clarify in depth the sources of the differences between control and schizophrenia patients.

Stimulus-driven (SDN) and goal-driven networks (GDN)

Our results and discussion about context-dependent effects permit the description of an initial framework of the general features involved in the number parity decision mixed with the auditory oddball task. We can take some features of our results and combine them with those in SDN and GDN of attention (Corbetta et al., 2002, 2008) and executive control with stimulus control, and contextual and episodic memory findings in Koechlin's group (Koechlin Ody, & Kouneiher, 2003, Koechlin & Summerfield, 2007) in the cortical areas in the human brain (see ***Figure 83*** at the top).

The experiment 1 (chapter 2) suggested that using several conditions may result in ERP changes related to memory effects or marking executive functions that modulate the orienting of attention. Although scalp EEG is ambiguous with regard to brain sources, these regions have resulted in a different explanation for the intertrial interval between novels, being more dorsal on the scalp (Fz and Pz) for schizophrenia patients showing a more goal-driven activation. On the other hand, for stimulus properties the regions on the scalp were more ventral (CP6 in ***Figure 83***) suggested showing a more stimulus-driven activation for the control group.

SDN and GDN are correlated across our contextual results, and they also showed an orienting of attention in the preceding novel stimulus not only in Experiment 1 with but also in Experiment 2 with fMRI, where the N.G vs G.G contrast showed the brain areas of the right hemisphere according to Corbetta's models (Corbetta et al., 2008). Another part of our

findings points to the different motor responses and reaching activity in Experiment 2. Moreover, features of the previous stimulus reflect episodic effects in the context of attention. We can interpret these issues as a raw temporal control of the P300 attention marker shown differently in the schizophrenic patients in Experiment 1 and modulated differently at different CTOAs in Experiment 4. Therefore there are consistencies with current theories of attention (see *Figure 83* at the bottom). In this way, a possible explanation of the different results of P300 marker is that there is a change of the activation in brain regions due to the preceding trials when the intertrial stimulus is not clearly significant. In *Figure 83* the sequence of the experiment consider past (red and yellow))and current events (green), this secuence has intrinsic properties that affects SDN and GDN. In yellow, the result of the preceding event with the stimulus driven markers suggested by the result of the stimulus properties. On the other hand, the left vertical arrow shows that the preceding and current stimulus in S1 are affecting the stimulus driven network as was suggested by the results of intertrial interval and the stimulus properties as well, as found in Experiment 4. Therefore, future studies we will come back and add or correct details to this proposed framework.

In summary, novel sound changes distract the participant. Using EEG and fMRI, the present results showed that determining the relevance of a sound prior to its occurrence can change the involuntary orienting of attention, which could conserve attentional sources for the task of relevance to the organism. Therefore, the different analysis done here provided evidence of a different goal-driven influence on brain areas on attention models (Corbetta et al., 2002, 2008) and electrophysiological responses in the different signatures for ERP waves associated with orienting and reorienting of attention.

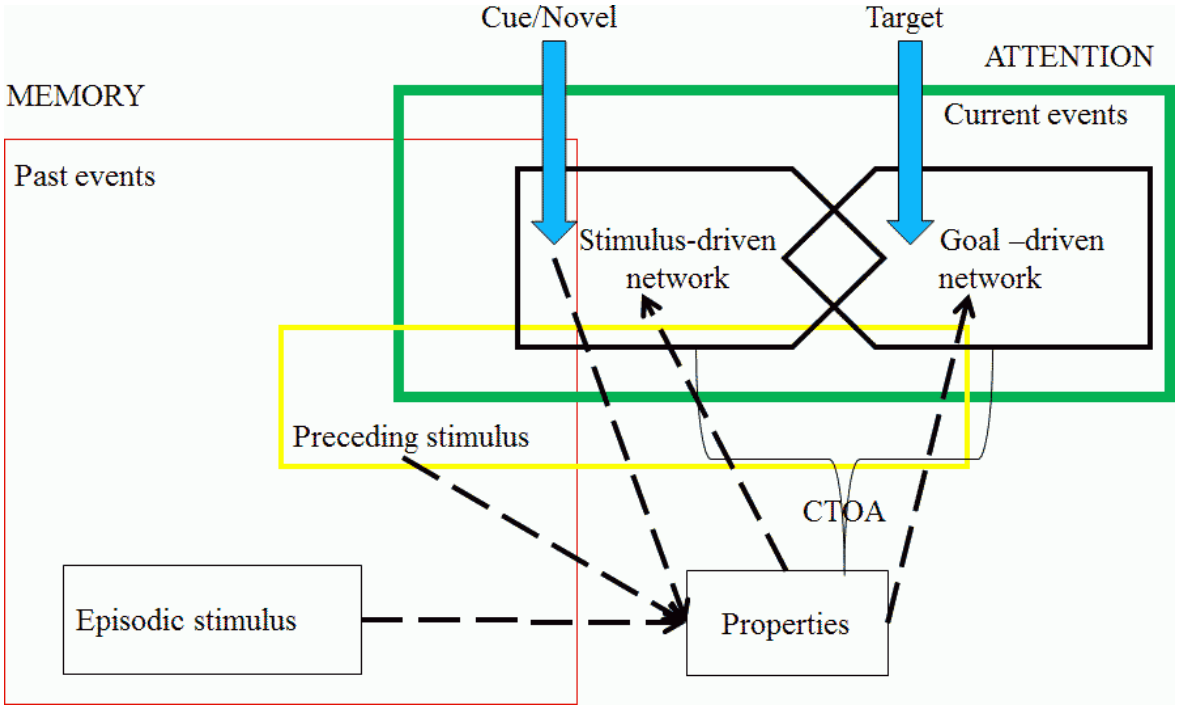


Figure 83 Attention processing of the number parity oddball task run in control participants and schizophrenic group. General superposition of key findings of the present experiments. Note that S2 (target) was not analysed in this way.

Other methods to study stimulus properties: Synchronization and coherence.

In the development of this dissertation, initially the single-trial analysis was presented to go later into LInear MOdelling data. But, there exist methods for studying the timing of the electrodes through the measures of consistency between the responses of the electrodes as those methods based on the EEG frequency bands that are not necessarily alpha, beta, delta or gamma bands (Burgess, 2012). For example, in schizophrenia patients Medkour and colleagues explored the characterization of functional connectivity widespread changes in patients with negative- and positive- syndrome schizophrenia. Their analisys relied on partial coherence between electrodes showed differences in the functional connectivity between these types of schizophrenia and from control as well (Medkour, Walden, Burgess, & Strelets, 2010). This study employed the method of Medkour based on partial coherence and

patterns of brain connectivity (Medkour, Walden, & Burgess 2009). This frequency approach may be used in different groups of participants in the experiments explored between controls and schizophrenia patients (chapter 2) and between the behaviourally distractible participants and the total group in the EEG/fMRI experiment (chapter 3). On the other hand, changes in the EEG theta rhythm recognition are associated with bigger spectral power in theta band for repeated words than for new words in the timing from 125 ms to 250 ms after stimulus presentation (Burgess & Gruzelier, 1997). Onton and colleagues used this theta analysis in ICA decomposition to study frontal midline theta responses in the frequencies from 5 to 7 Hz in experiment employing a letter memory task. Results suggested adjustment in frontal electrodes to trial per trial basis without activity difference between shorter and longer stimulus presentation (Onton, Delorme, & Makeig, 2005). Also, earlier evidence of different auditory processing electrodes in schizophrenia patients suggested a different interhemispheric information transfer (McKay, Headlam, & Kopolov, 2000). Henshall and colleagues tested different bands in these interhemispheric difference finding, they explored auditory hallucinations in an auditory task composed by frequency tones and words, participants were asked to inform any auditory hallucination during the experimental task. They found that the EEG coherence is different between correspondent electrodes close to auditory cortex in different beta bands (Henshall, Sergejew, Rance, McKay, & Copolov, 2013). In Chapters 4 and 5, the experiments were playing with different CTOAs where stimulus properties were shown differently at shorter and longer CTOAs, therefore relative changes between novel and standard stimulus explored by means of stimulus properties may be explain of power in EEG responses across electrodes and possibly in different range times after stimulus onset. Moreover, in chapter 3, in the simultaneous EEG and fMRI experiment the EEG analysis may be correlated at different spectral bands with the FEF.

Revisiting the tree of problems.

The present study was conducted with regard to the tree of problems presented in the introduction, bearing in mind the following: (30) spatial EEG limitation, dividing the analysis in frontal, parietal, occipital and hemispheric scalp lateralization; (20) temporal fMRI limitation, using contrasts and, in general, that the point of view of analysis was optimised bearing in mind the use of the single trial analysis in EEG and the previous context in both EEG and fMRI to (40) integrate the results of different experiments. While all the previous combinations helped to define better the (50) dynamics of the response to the attention task, the associated brain areas were not elucidated due to the problems in the simultaneous analysis in EEG and fMRI. On the other hand, the parity number in response to auditory paradigm has been tested and partially explain the (70) management of attention biomarkers through the analysis of several stimulus properties in the context and episodic timecourse. These have improved the (80) understanding about brain responses and how time and the properties of the stimuli improve the understanding of the orientation of attention (ISI and CTOA). Moreover, this research has provided a small contribution to the understanding of certain patterns observed in (90) schizophrenia patients related to two stimulus interaction in the attention reorienting process.

Points of view and limitations

Returning to the psychological level discussed in the introduction, the TTG was considered in the fMRI experiment. This region possibly extends the visual control and reorienting model of Corbetta and colleagues to the auditory modality (Corbetta et al., 2002, 2008). However, more analysis is required to assure that this model may be extended to other modalities, for example studies in the auditory modality in the different experiments and analysis that formed a part of this thesis helped to gain a better understanding about the influence of the

stimulus properties and time of presentation of each stimulus. As stated in the discussion in Chapter 3, it is possible that DCM may help to enforce that. On the other hand, subcortical regions such as the TRN are not accessible by EEG & fMRI measures. This limitation was not addressed here, but although Mulert and colleagues highlighted the difficulties in undertaking a study on subcortical structures, they suggested that TRN is involved in N100 and gamma frequency response band (Mulert et al., 2007). Other deeper regions are also possible, such as the Thalamuspulvinar. Our results in the fMRI analysis in Chapter 3 supported the idea that the Right ThalamusPulvinar has a role in the processing and possibly in the regulation of Novel signals in Goal and Non-Goal tasks in auditory tasks. Finally, the psychological level of the number decision task was not explored in detail, *i.e.* The range of time of Goal was not studied in depth in the present experiments. Recent evidence suggest the SNARC effect is locally stable in each participant (Viarouge, Hubbard, & McCandliss, 2014). Moreover, van Dijck studies on working memory studies on the context of parity task complemente the view of Viarouge (van Dijck, Gevers, & Fias, 2011; van Dijck, Gevers, & Fias, 2009). Therefore, these recent evidences may be considered to study in depth the Goal decision part of the present experiments.

Returning to the algorithm level discussed in the introduction, the experiments and simulations undertaken in this thesis suggest we should analyse the compromise between task duration (*i.e.* number of trials and number of novel events), contextual effect in terms of the previous events and subjectivity of the participant against the task switching. On the other hand, although the arousal response was not addressed here, the arousal response of the participant influences brain activations where TRN is believed to play a transmission role in "the sleeping and aroused brain" (Steriade et al. 1993). Throughout the present experiments we emphasized the contextual effect, considering either the previous cue or the previous

target. Specific changes should depend on the nature of the stimulus introduced, as found in the EEG analysis discussed in Chapter 2. A limitation to previous studies (e.g. CTOA at 300 ms) was found when the simulation discussed in Chapter 4 and the experimental results discussed in Chapter 5 suggest that a further reference in terms of the information state such as the CTOA less than 250 ms or more than 400 ms. This CTOA reference possibly would extend the typical neutral condition to another temporal neutral condition. At this point both inmediate context signal and the changes CTOA are making a sort of reference as the main point of view in most of the results and discussions done in this work.

Returning to the biological level discussed in the introduction, we can compare our experimental task load with a weight load in a physical experience: when we have more weight in a lift, as a stimulus, it would take more time to habituate to a heavier or more frequent stimulus. Therefore, we expected to see a developed habituation depending on the inter-stimuli interval and we expect to have the same response when the energy of the sound is similar, i.e. Polich prediction of the larger local probability the larger P300 changes should be confirmed when we normalize sounds in the experiment (Polich, 2007). Thus, when conditions were changing continuously we would expect a slow adaptation or an irregular basis and moreover when the CTOA is affecting information such as the EEG experiment with CTOA at 300 ms as discussed in Chapter 2. We can also say that temporal sequence is important, for example in muscle events where habituation depends on the rhythms of the stimulus sequence as was studied at 2 different CTOA in Chapter 5. In this way, further studies may extend Corbetta's model for attention (Corbetta et al, 2002, 2008).

Returning to the technological level discussed in the introduction, in the simultaneous EEG and fMRI there were problems due to electrical noise produced by the stimuli and operating

differently in several channels (shown in Chapter 4). On the other hand, the brain in a different environment, such as the MRI, may answer differently. Roberts and colleagues explained that due to the magneto-hydrodynamic fluid forces the fluid that has contact with hair cells make changes by pressure in the signal transduction on both left and right inner ears. Then the signal is going to the of the left when the head is pitched up, suggesting that this is following the Lorenz Law; they also studied horizontal eye movements as well as a cause of vertigo in MRI (Roberts, Marcelli, Gillen, Carey & Della-Santina, 2011). Moreover, the cerebrospinal fluid (CSF) is more conductive than the gray matter, white matter and skull (Oostendorp, Delbeke & Stegeman, 2000). This CSF layer changes between 2 mm and 3 mm from prone to supine position and this changes around 30 % the scalp EEG power (Rice, Rorden, Little, & Parra, 2013), which is an extra issue when we want to compare results for an experimental task when the participant is sitting in an armchair or lying in a supine or prone position. This participant position is an issue that can be kept in mind not only to analyse across offline multimodal experiments but also in favour of the simultaneous EEG and fMRI experiment. Indeed, this was not addressed in the thesis due to the artefact of the headphones in the EEG measures at the precise time that the sound stimulus is presented as was addressed in Chapter 2.

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